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(54) Title: NOVEL ANTI-INFECTIVES

(57) Abstract: Disclosed are compounds useful as HCV anti-infectives and methods of making and using the same.

NOVEL ANTI-INFECTIVES

FIELD OF THE INVENTION

The present invention relates to compounds that inhibit an RNA-containing virus and methods of making and using the same. Specifically, the present invention relates to inhibitors of hepatitis C virus (HCV).

BACKGROUND OF THE INVENTION

In the U.S., an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have been estimated at $5.46 billion for the U.S. in 1997. Worldwide, over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/yr. by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Alpha-interferon (alone or in combination with ribavirin) has been widely used since its approval for treatment of chronic HCV infection. However, adverse side effects are commonly associated with this treatment: flu-like symptoms, leukopenia, thrombocytopenia, and depression from interferon, as well as hemolytic anemia induced by ribavirin (Lindsay, K.L. (1997) Hepatology 26 (Suppl. 1):71S-77S). This therapy remains less effective against infections caused by HCV genotype 1 (which constitutes ~75% of all HCV infections in the developed markets) compared to infections caused by the other 5 major HCV genotypes. Unfortunately, only ~50-80% of the patients respond to this treatment (measured by a reduction in serum HCV RNA levels and normalization of liver enzymes) and, of those treated, 50-70% relapse within 6 months of cessation of treatment. Recently with the introduction of pegylated interferon (Peg-IFN), both initial and sustained response rates have improved substantially, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy and the impaired response in patients with genotype 1 present opportunities for improvement in the management of this disease.

First identified by molecular cloning in 1989 (Choo, Q-L. *et al.*, (1989) Science 244:359-362), HCV is now widely accepted as the most common causative agent of post-transfusion non A, non-B hepatitis (NANBH) (Kuo,G. *et al.*, (1989) Science 244:362-364).

Due to its genome structure and sequence homology, this virus was assigned as a new genus in the *Flaviviridae* family. Like the other members of the *Flaviviridae* (such as flaviviruses (e.g., yellow fever virus and Dengue virus types 1-4) and pestiviruses (e.g., bovine viral diarrhea virus, border disease virus, and classic swine fever virus (Choo *et al.*, 1989; Miller, R.H. and R.H. Purcell (1990) Proc. Natl. Acad. Sci. USA 87:2057-2061)), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang, C.Y., Le, S.Y., Ali, N., Siddiqui, A., Rna-A Publication of the Rna Society. 1(5): 526-537, 1995 Jul). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

Upon entry into the cytoplasm of the cell, the HCV-RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded proteinases (Rice, C.M. (1996) in B.N. Fields, D.M.Knipe and P.M. Howley (Eds.) Virology, 2nd Edition, p931-960, Raven Press, NY). Following the termination codon at the end of the long ORF, there is a 3' NTR which roughly consists of three regions: an ~ 40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the "3' X-tail" (Kolykhalov, A. et al., (1996) J. Virology 70:3363-3371; Tanaka, T. et al., (1995) Biochem Biophys. Res. Commun. 215:744-749; Tanaka, T. et al., (1996) J. Virology 70:3307-3312; Yamada, N. et al., (1996) Virology 223:255-261). The 3' NTR is predicted to form a stable secondary structure that is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E., et al., (1996) EMBO J. 15:12-22), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype 1a and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (Kolykhalov, A.A., et al., (2000) J.

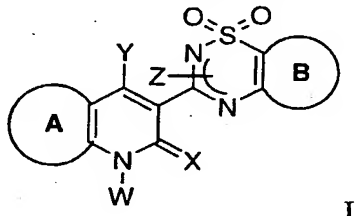
Virology 74:2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to cure HCV infection.

Positive strand hepatitis C viral RNA is the nucleic acid strand that is translated and initially copied upon entry of the HCV-RNA into the cell. Once in the cell, positive strand viral RNA generates a negative strand replicative intermediate. Negative strand RNA is the template used to generate the positive strand message that is generally packaged into productive virions. Presently, HCV inhibitor compounds are only evaluated for their ability to inhibit positive strand HCV-RNA. However, it would be desirable to develop inhibitor compounds having the ability to inhibit both positive and negative strand replication to obtain complete clearance of the HCV virus.

Accordingly, there exists a significant need to identify synthetic or biological compounds for their ability to inhibit HCV. Preferably, such synthetic or biological compounds inhibit both positive and negative strand replication of the hepatitis C virus.

SUMMARY OF THE INVENTION

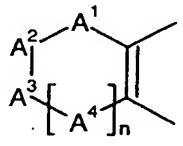
This invention is directed to compounds having Formula I, as follows:



I

wherein:

A is an accessible fused ring moiety that is an aromatic 6-membered carbocyclic ring moiety or a saturated, unsaturated or aromatic 5 or 6-membered heterocyclic ring moiety, wherein said heterocyclic ring moiety contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, represented by Formula II:



II

where:

A^1 is $CR_A{}^1$, $CHR_A{}^1$, N, $NR_{A1}{}^5$, O or S;

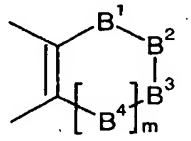
A^2 is $CR_A{}^2$, $CHR_A{}^2$, N, $NR_{A2}{}^5$, O or S;

A^3 is CR_A^3, CHR_A^3, N, NR_{A3}^5, O or S;

A^4 is CR_A^4, CHR_A^4, N, NR_{A4}^5, O or S;

n is 0 or 1;

B is an accessible fused ring moiety that is a 6-membered aromatic carbocyclic ring moiety or a saturated, unsaturated or aromatic 5 or 6-membered heterocyclic ring moiety, wherein said heterocyclic ring moiety contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, represented by the Formula III:



III

where:

B^1 is CR_B^1, CHR_B^1, N, NR_{B1}^5, O or S;

B^2 is CR_B^2, CHR_B^2 N, NR_{B2}^5, O or S;

B^3 is CR_B^3, CHR_B^3, N, NR_{B3}^5, O or S;

B^4 is CR_B^4, CHR_B^4, N, NR_{B4}^5, O or S;

m is 0 or 1;

or an N- or S-oxide thereof, provided that A and B are not both phenyl ring moieties, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof; wherein:

R_A^1 is hydrogen, halogen, C_1-C_4 alkyl, $-OR^{12}$, $-SR^{12}$, $-NR^{11}R^{12}$, -C(O)OH, $-C(O)NHR^{12}$, cyano or nitro;

R_A^2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, heterocycloalkyl, nitro, cyano, halogen, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-NR^{10}R^{11}$, protected -OH, $-N(R^{11})C(O)R^{10}$, $-OC(O)NR^{10}R^{11}$, $-N(R^{11})C(O)NR^{10}R^{11}$, $-P(O)(OR^{10})_2$, $-SO_2NR^{10}R^{11}$, $-SO_3H$, or $-N(R^{11})SO_2R^{13}$,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-NR^{11}R^{12}$, cyano, nitro, $-CO_2R^{11}$, $-C(O)OC_1$-C_4 alkyl, $-CONR^{11}R^{12}$, $-CONH_2$, aryl, and heteroaryl,

and where said cycloalkyl, heterocycloalkyl, aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -OH, -SH, $-NH_2$, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl,

-N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano, nitro, -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl) and -$CONH_2$;

R_A^3 is hydrogen, halogen, cyano, C_1-C_6 alkyl, -OH, or -CO_2H;

R_A^4, R_B^4 and R_B^3 are each independently selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6 alkyl, -OH, and -OC_1-C_4 alkyl;

R_B^1 is hydrogen, halogen, C_1-C_4 alkyl, -OR^{10} or oxo;

R_B^2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, nitro, cyano, halogen, -C(O)OR^{10}, -C(O)R^{10}, -C(O)$NR^{10}R^{11}$, -OR^{10}, -SR^{10}, -S(O)R^{13}, -$S(O)_2R^{13}$, -$NR^{10}R^{11}$, protected -OH, -N(R^{11})C(O)R^{10}, -OC(O)$NR^{10}R^{11}$, -N(R^{11})C(O)$NR^{10}R^{11}$, -P(O)$(OR^{10})_2$, -$SO_2NR^{10}R^{11}$, -SO_3H, or -N(R^{11})SO_2R^{13},

where said C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -$NR^{11}R^{12}$, cyano, nitro, -CO_2H, -C(O)OC_1-C_4 alkyl, -$CONR^{11}R^{12}$, -$CONH_2$, aryl, heteroaryl, heterocycloalkyl, -C(O)aryl, -C(O)heterocycloalkyl, and -C(O)heteroaryl, where said aryl, heteroaryl, heterocycloalkyl, aryl, -C(O)aryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OH, -SH, -NH_2, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano and nitro,

and where said cycloalkyl, heterocycloalkyl, aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -OH, -SH, -NH_2, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano, nitro, -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl) and -$CONH_2$;

or optionally, when A or B is an accessible heterocyclic ring moiety, one or more of R_A^1, R_A^2, R_A^3, R_A^4, R_B^1, R_B^2, R_B^3 and R_B^4 is oxo;

R_{A1}^5, R_{A3}^5, R_{A4}^5, R_{B1}^5, R_{B3}^5, R_{B4}^5 are each independently selected from: hydrogen, C_1-C_4 alkyl, -CO_2H, -$CONH_2$, -CO_2C_1-C_4 alkyl, -C(O)C_1-C_4 alkyl, -CONH(C_1-C_4 alkyl) and -C(O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl);

R_{A2}^5 and R_{B2}^5 is independently selected from the group consisting of H, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, -C(O)OR^{10}, -C(O)R^{10}, -S(O)R^{13}, -$S(O)_2R^{13}$, -$CONR^{10}R^{11}$, -P(O)$(OR^{10})_2$ and -$SO_2NR^{10}R^{11}$, where said alkyl, alkenyl, alkynyl,

cycloalkyl or aryl group is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halogen, cyano, $-OR^{10}$, $-SR^{10}$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-CONR^{10}R^{11}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$ and $-SO_2NR^{10}R^{11}$; wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -CN and $-NO_2$;

W is hydrogen, $-C(O)OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkenyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkynyl)-(C_3-C_6 cycloalkyl), -(C_1-C_6 alkyl)-heterocycloalkyl, -(C_2-C_6 alkenyl)-heterocycloalkyl, -(C_2-C_6 alkynyl)-heterocycloalkyl, -(C_1-C_6 alkyl)-aryl, (C_2-C_6 alkenyl)-aryl, -(C_2-C_6 alkynyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl, -(C_2-C_6 alkenyl)-heteroaryl, or -(C_2-C_6 alkynyl)-heteroaryl,

where said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, -OH, $-OC_1$-C_4 alkyl, -SH, $-SC_1$-C_4 alkyl, -S(O)(C_1-C_4 alkyl), $-SO_3H$, and $-S(O)_2$(C_1-C_4 alkyl),

said C_3-C_6 cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_4 alkyl, -OH, $-OC_1$-C_4 alkyl, -SH, $-SC_1$-C_4 alkyl, -S(O)(C_1-C_4 alkyl), $-SO_3H$, and $-S(O)_2$(C_1-C_4 alkyl),

and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of said -(C_1-C_6 alkyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkenyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkynyl)-(C_3-C_6 cycloalkyl), -(C_1-C_6 alkyl)-heterocycloalkyl, -(C_2-C_6 alkenyl)-heterocycloalkyl, -(C_2-C_6 alkynyl)-heterocycloalkyl, -(C_1-C_6 alkyl)-aryl, (C_2-C_6 alkenyl)-aryl, -(C_2-C_6 alkynyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl, -(C_2-C_6 alkenyl)-heteroaryl, or -(C_2-C_6 alkynyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, cyano, nitro, -OH, $-NH_2$, $-OC_1$-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -NH(C_1-C_4 alkyl);

X is O or S;

Y is -OH or -SH;

Z is hydrogen or C_1-C_4 alkyl;

wherein each R^{10} is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl,

and -C_1-C_6 alkyl-heteroaryl, -C_2-C_6 alkenyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkenyl-heterocycloalkyl, -C_2-C_6 alkenyl-aryl, -C_2-C_6 alkenyl-heteroaryl, -C_2-C_6 alkynyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkynyl-heterocycloalkyl, -C_2-C_6 alkynyl-aryl, and -C_2-C_6 alkynyl-heteroaryl,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OR^{12}, -$NR^{11}R^{12}$, cyano, nitro, -CO_2R^{12}, -$CONR^{11}R^{12}$, -$NR^{11}CONR^{11}R^{12}$, -$OCONR^{11}R^{12}$, -$SO_2NR^{11}R^{12}$, and -COR^{12},

and where any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl (including the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moieties of said -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, or -C_1-C_6 alkyl-heteroaryl) is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OR^{12}, -$NR^{11}R^{12}$, cyano, nitro, -CO_2R^{12}, -$CONR^{11}R^{12}$, -$NR^{11}CONR^{11}R^{12}$, -$OCONR^{11}R^{12}$, -$SO_2NR^{11}R^{12}$, and -COR^{12};

each R^{11} is independently selected from hydrogen and C_1-C_6 alkyl;

each R^{12} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_4 alkyl-C_3-C_8 cycloalkyl, -C_1-C_4 alkyl-heterocycloalkyl, -C_1-C_4 alkyl-aryl, or -C_1-C_4 alkyl-heteroaryl

where said cycloalkyl, heterocycloalkyl, aryl , heteroaryl, -alkylcycloalkyl, -alkylheterocycloalkyl, -alkylaryl or -alkylheteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen -OC_1-C_6 alkyl, -OC_1-C_6 haloalkyl, cyano, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2C_1-C_6 alkyl, -CO_2H, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), and -$CONH_2$;

or, when present in any $NR^{10}R^{11}$ or $NR^{11}R^{12}$, each R^{10} and R^{11} or each R^{11} and R^{12}, independently, taken together with the nitrogen to which they are attached represent a 3-6-membered saturated ring optionally containing one other heteroatom selected from oxygen and nitrogen, where said 3-6-membered ring is unsubstituted or substituted with one or more substituents independently selected from hydrogen, C_1-C_6 alkyl, halogen, cyano, -OC_1-C_6 alkyl, -OH, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2H, -C(O)OC_1-C_6 alkyl, -C(O)C_1-C_6 alkyl, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), -$CONH_2$, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl,

C_3-C_6 cycloalkyl-C_1-C_6 alkyl-, heterocycloalkyl-C_1-C_6 alkyl-, aryl-C_1-C_6 alkyl- and heteroaryl-C_1-C_6 alkyl-, and where said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl-, heterocycloalkylalkyl-, arylalkyl- or heteroarylalkyl- is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen -OC_1-C_6 alkyl, -OC_1-C_6 haloalkyl, cyano, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2C_1-C_6 alkyl, -CO_2H, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), and -$CONH_2$;

each R^{13} is independently selected from the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, and -C_1-C_6 alkyl-heteroaryl, -C_2-C_6 alkenyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkenyl-heterocycloalkyl, -C_2-C_6 alkenyl-aryl, -C_2-C_6 alkenyl-heteroaryl, -C_2-C_6 alkynyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkynyl-heterocycloalkyl, -C_2-C_6 alkynyl-aryl, and -C_2-C_6 alkynyl-heteroaryl,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OR^{14}, -$NR^{11}R^{14}$, cyano, nitro, -CO_2R^{14}, -$CONR^{11}R^{14}$, -$NR^{11}CONR^{11}R^{14}$, -$OCONR^{11}R^{14}$, -$SO_2NR^{11}R^{14}$, and -COR^{14},

and where any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl (including the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moieties of said -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, or -C_1-C_6 alkyl-heteroaryl) is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OR^{14}, -$NR^{11}R^{14}$, cyano, nitro, -CO_2R^{14}, -$CONR^{11}R^{14}$, -$NR^{11}CONR^{11}R^{14}$, -$OCONR^{11}R^{14}$, -$SO_2NR^{11}R^{14}$, and -COR^{14};

each R^{14} is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, and -C_1-C_6 alkyl-heteroaryl;

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

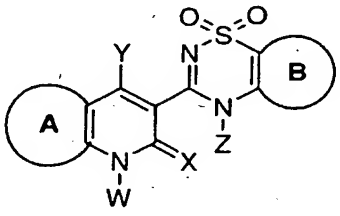
This invention is also directed to a prodrug of a compound according to Formula I, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof. In addition, this invention is directed to pharmaceutical compositions comprising a compound according to Formula I, or a tautomer thereof, or a prodrug thereof, or salts or solvates thereof.

In another embodiment, this invention is directed to a method of inhibiting an RNA-containing virus comprising contacting the virus with an effective amount of a compound of Formula I. In yet another embodiment, this invention is directed to a method of treating infection or disease caused by an RNA-containing virus which comprises administering to a subject in need thereof, an effective amount of a compound according to Formula I. This invention is particularly directed to methods of inhibiting hepatitis C virus. This invention is also directed to a method for inhibiting replication of hepatitis C virus that comprises inhibiting replication of both positive and negative strand HCV-RNA.

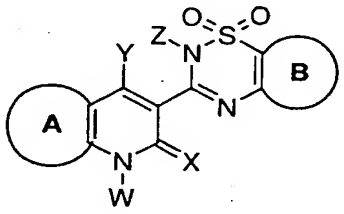
In yet another embodiment, this invention is directed to the use of a compound of Formula I, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of an RNA-containing virus. Particularly, this invention is directed to the use of a compound of Formula I, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament that inhibits hepatitis C virus. More particularly, this invention is directed to the use of a compound of Formula I, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament that inhibits replication of both positive and negative strand HCV-RNA.

DETAILED DESCRIPTION OF THE INVENTION

It will be appreciated by those skilled in the art that the compounds of this invention, represented by generic Formula I, above, exist in tautomeric forms having Formula I-A and Formula I-B, as follows:



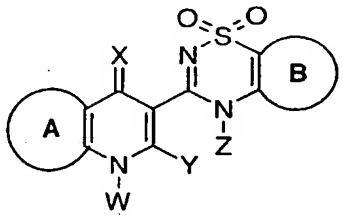
I-A



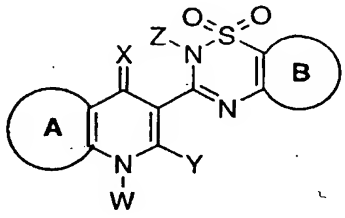
I-B

In addition, it will be appreciated by those skilled in the art, that the compounds of this invention may exist in several other tautomeric forms. All tautomeric forms of the compounds described herein are intended to be encompassed within the scope of the present

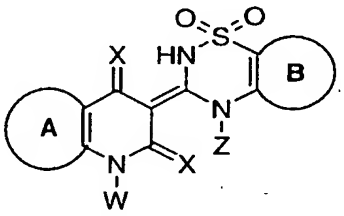
invention. Examples of some of the other possible tautomeric forms of the compounds of this invention include, but are not limited to:



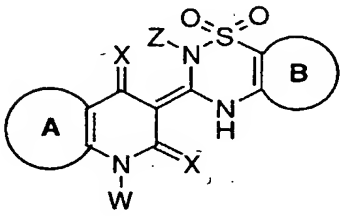
I-C



I-D



I-E



I-F

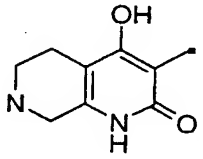
As a convention, the compounds exemplified herein have been assigned names based on the structure of the tautomer of Formula I-A. It is to be understood that any reference to named compounds of this invention is intended to encompass all tautomers of the named compounds and any mixtures of tautomers of the named compounds.

In the compounds of this invention, groups A and B are defined as accessible fused ring moieties. As used herein, an accessible fused ring moiety refers to a ring moiety that is fused to the pyridonyl or thiadiazinyl moiety of Formula I (fused ring moiety A and B, respectively) and forms a bicyclic ring moiety that is stable and that may be synthesized by one skilled in the art. The double bond present in the pyridonyl and/or thiadiazinyl ring moiety is not considered in the characterization of a fused ring moiety as saturated or unsaturated. With regard to the characterization of the fused ring moieties, the terms saturated and unsaturated only describe whether the 3 or 4 atom A^{1-4} or B^{1-4} moiety is saturated or unsaturated. The double bond present in the pyridonyl and/or thiadiazinyl ring moiety is included when characterizing a fused ring moiety as aromatic. In addition, it will be understood by those skilled in the art that when an A or B fused ring moiety is unsaturated or aromatic, the fused ring moiety contains at least one double bond moiety selected from –CH=CH-, -CR=CH-, -CR=CR-, -N=CH-, -N=CR- and –N=N- (i.e., at least

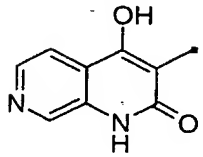
two of A^{1-4} or B^{1-4} is selected from CH, CR and N). Fused ring moieties are exemplified by the following:

Group A fused ring moiety:

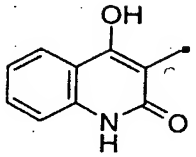
saturated



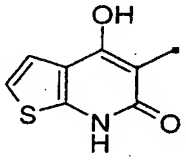
aromatic



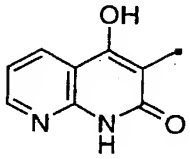
phenyl:



thienyl:

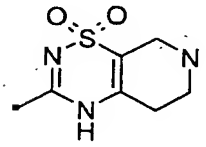


pyridyl:

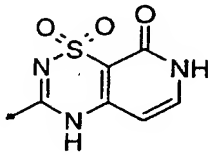


Group B fused ring moiety:

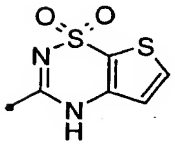
saturated

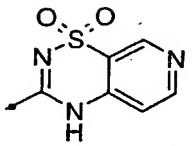


unsaturated

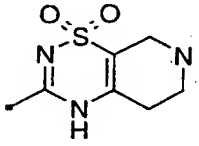


aromatic

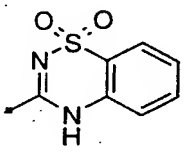




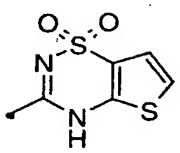
piperidyl



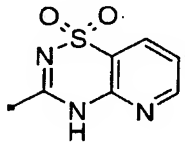
phenyl:



thienyl:

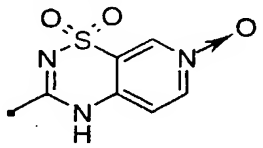


pyridyl:



As provided herein, an accessible A or B fused ring moiety may optionally comprise an oxide of a heteroatom of a heterocyclic ring moiety, specifically an oxide of N

or S. Such oxides include N→O, S→O, and SO_2 moieties that form stable, accessible compounds. An example of such an oxide-containing fused ring moiety is:



As used herein, the term "alkyl" represents a straight-or branched-chain saturated hydrocarbon, which may be unsubstituted or substituted by one, or more of the substituents defined herein. Exemplary alkyls include, but are not limited to methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl and pentyl. The term "lower alkyl" refers to an alkyl containing from 1 to 4 carbon atoms.

When the term "alkyl" (or alkenyl or alkynyl) is used in combination with other substituent groups, such as "haloalkyl" or "arylalkyl", the term "alkyl" is intended to encompass a divalent straight or branched-chain hydrocarbon radical. For example, "cycloalkylalkyl" is intended to mean the radical -alkyl-cycloalkyl, wherein the alkyl moiety thereof is a divalent straight or branched-chain hydrocarbon radical and the cycloalkyl moiety thereof is as defined herein, and is represented by the bonding arrangement present in the groups –CH_2-cyclopropyl, -CH_2-cyclohexyl, or -$CH_2(CH_3)CHCH_2$-cyclopentenyl. "Arylalkyl" is intended to mean the radical –alkylaryl, wherein the alkyl moiety thereof is a divalent straight or branched-chain carbon radical and the aryl moiety thereof is as defined herein, and is represented by the bonding arrangement present in a benzyl group (-CH_2-phenyl).

As used herein, the term "alkenyl" represents a straight-or branched-chain hydrocarbon containing one or more carbon-carbon double bonds. An alkenyl may be unsubstituted or substituted by one or more of the substituents defined herein. Exemplary alkenyls include, but are not limited ethenyl, propenyl, butenyl, isobutenyl and pentenyl.

As used herein, the term "alkynyl" represents a straight-or branched-chain hydrocarbon containing one or more carbon-carbon triple bonds and, optionally, one or more carbon-carbon double bonds. An alkynyl may be unsubstituted or substituted by one or more of the substituents defined herein. Exemplary alkynyls include, but are not limited ethynyl, butynyl, propynyl (propargyl, isopropynyl), pentynyl and hexynyl.

"Cycloalkyl" represents a group or moiety comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 3 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents defined herein and may be

saturated or partially unsaturated. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl and cycloheptyl.

"Heterocycloalkyl" represents a group or moiety comprising a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or partially unsaturated, containing 3 to 18 ring atoms, which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents defined herein. Illustrative examples of heterocycloalkyls include, but are not limited to, azetidinyl, pyrrolidyl (or pyrrolidinyl), piperidinyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl (or tetrahydrofuranyl), dihydrofuryl, oxazolinyl, thiazolinyl, pyrazolinyl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3.0]nonyl, oxabicylo[2.2.1]heptyl and 1,5,9-triazacyclododecyl. Generally, in the compounds of this invention, heterocycloalkyl is a monocyclic heterocycloalkyl, such as azetidinyl, pyrrolidyl (or pyrrolidinyl), piperidyl (or piperidinyl), piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl (or tetrahydrofuranyl), tetrahydrothienyl, dihydrofuryl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathianyl, 1,3-dithianyl, oxazolinyl, thiazolinyl and pyrazolinyl.

"Aryl" represents a group or moiety comprising an aromatic, monovalent monocyclic or bicyclic hydrocarbon radical containing from 6 to 10 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents defined herein, and to which may be fused one or more cycloalkyl rings, which may be unsubstituted or substituted by one or more substituents defined herein. Generally, in the compounds of this invention, aryl is phenyl.

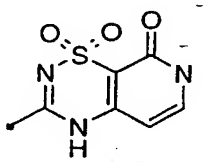
"Heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic, bicyclic, or tricyclic radical, containing 5 to 18 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents defined herein. This term also encompasses bicyclic or tricyclic heterocyclic-aryl compounds containing an aryl ring moiety fused to a heterocycloalkyl ring moiety, containing 5 to 16 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents defined herein. Illustrative examples of heteroaryls include, but

are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl (or furanyl), isothiazolyl, furazanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridyl (or pyridinyl), pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, tetrazolyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuryl, 2,3-dihydrobenzofuryl, chromenyl, chromanyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthridinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, carbozolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenathiazinyl, and phenoxazinyl. Generally, in the compounds of this invention, heteroaryl is a monocyclic heteroaryl, such as thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl and tetrazolyl.

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Hydroxy" or "hydroxyl" are intended to mean the radical –OH. "Alkoxy" is intended to mean the radical $-OR_a$, where R_a is an optionally substituted alkyl group. Exemplary alkoxy include methoxy, ethoxy, propoxy, and the like. "Lower alkoxy" groups have optionally substituted alkyl moieties from 1 to 4 carbons. "Cyano" is intended to mean the radical -CN. "Amino" is intended to mean the radical $-NH_2$. "Alkylenedioxy" is intended to mean the divalent radical $-OR_aO-$ which is bonded to adjacent atoms (e.g., adjacent atoms on a phenyl or naphthyl ring), wherein R_a is a C_1-C_2 alkyl group. Exemplary alkylenedioxy-substituted phenyls include benzo[1,3]dioxyl and 2,3-dihydro-benzo[1,4]dioxyl.

The term "oxo" is intended to refer to a diradical keto moiety, =O. As provided herein, when A or B is an accessible heterocyclic ring moiety, one or more of R_A^1, R_A^2, R_A^3, R_A^4, R_B^1, R_B^2, R_B^3 and R_B^4 may be oxo. Such oxo-containing heterocyclic ring moieties are well known. For example, when A or B is a piperidyl fused ring moiety and one of R_A^1, R_A^2, R_A^3, R_A^4, R_B^1, R_B^2, R_B^3 or R_B^4 is oxo, the resulting A or B moiety is a piperidonyl fused ring moiety. When A or B is an aromatic heterocyclic fused ring moiety (e.g., pyridyl or pyrazolyl), the resulting oxo-containing heterocyclic moiety (e.g., pyridonyl or pyrazolonyl, respectively) may result from tautomerization of the corresponding hydroxy-substituted heterocycle, that is, in one tautomeric form of the compound R_A^1, R_A^2, R_A^3, R_A^4, R_B^1, R_B^2, R_B^3 or R_B^4 is hydroxyl and in another tautomeric form R_A^1, R_A^2, R_A^3, R_A^4, R_B^1, R_B^2, R_B^3 or R_B^4 is oxo. It is to be understood that all tautomeric structures of the compounds described herein are intended to be encompassed within the scope of this invention. Accordingly,

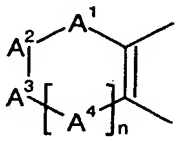
such oxo-containing tautomers are intended to be encompassed whether R_A^1, R_A^2, R_A^3, R_A^4, R_B^1, R_B^2, R_B^3 or R_B^4 is defined as hydroxyl or oxo (OH or =O). An example of such an oxo-containing fused ring moiety is :



This invention is directed to compounds of Formula I wherein A and B are each a fused ring moiety independently selected from a phenyl, pyridyl, piperidyl, pyridazinyl, pyrimidinyl, pyrazolinyl, thiazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, triazinyl, isothiazolyl or thiadiazolyl ring moiety, provided that A and B are not both fused phenyl ring moieties.

In one embodiment of the compounds, tautomers, pharmaceutically acceptable salts or solvates of this invention according to Formula I, above,

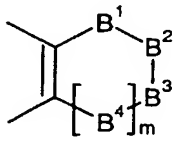
A is a fused ring moiety selected from a phenyl, pyrazolyl, pyridyl or thienyl ring moiety represented by



II

where when n is 0, A^1 is CR_A^1 or S, A^2 is CR_A^2, NH or N, and A^3 is CR_A^3, N, NR_{A3}^5 or S; or when n is 1, A^1 is CR_A^1, A^2 is CR_A^2, A^3 is CR_A^3, and A^4 is CR_A^4 or N; and

B is a fused ring moiety selected from a phenyl, pyridyl, piperidyl, thienyl or pyrazolyl ring moiety represented by



III

where when m is 0, B^1 is CR_B^1, B^2 is CR_B^2, NH or N, and B^3 is N, NR_{B3}^5 or S; or when m is 1; B^1 is CR_B^1 or CHR_B^1, B^2 is CR_B^2, CHR_B^2, N, N→O or NR_{B2}^5, B^3 is CR_B^3 or CHR_B^3, and B^4 is CR_B^4, CHR_B^4, or N;

or an N-oxide thereof, provided that A and B are not both phenyl ring moieties, wherein R_A^1, R_A^2, R_A^3, R_A^4, R_{A3}^5, R_B^1, R_B^2, R_B^3, R_B^4 and R_{B2}^5 are as defined herein.

In the specific embodiments of the compounds of this invention, X is O; Y is OH; and Z is H.

In another embodiment of this invention, R_A^1 is hydrogen, halogen or C_1-C_4 alkyl. In other embodiments, R_A^1 is hydrogen or halogen. In specific embodiments of this invention, R_A^1 is H.

In yet another embodiment of this invention, R_A^2 is hydrogen, C_1-C_4 alkyl, nitro, cyano, halogen, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-NR^{10}R^{11}$, $-N(R^{11})C(O)R^{10}$, $-OC(O)NR^{10}R^{11}$, $-N(R^{11})C(O)NR^{10}R^{11}$, $-P(O)(OR^{10})_2$, $-SO_2NR^{10}R^{11}$, $-SO_3H$, or $-N(R^{11})SO_2R^{13}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-NR^{11}R^{12}$, cyano, nitro, $-C(O)R^{10}$, $-CO_2R^{11}$, $-C(O)OC_1$-C_4 alkyl, $-CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl. In other embodiments, R_A^2 is hydrogen, halogen, $-OR^b$ or $-NHR^b$, where R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -OH, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CONH(C_1$-C_2 alkyl) and 5-6 membered heterocycloalkyl or heteroaryl. In specific embodiments, R_A^2 is H, Br, F, -OH or $-OCH_2CN$.

In another embodiment of this invention, R_A^3 is hydrogen, halogen, C_1-C_4 alkyl or $-CO_2H$. In other embodiments, R_A^3 is H, halogen, or C_1-C_4 alkyl. In specific embodiments, R_A^3 is H.

In a further embodiment of this invention, R_A^4 is hydrogen, halogen or C_1-C_4 alkyl. In other embodiments, R_A^4 is hydrogen.

In another embodiment of this invention, R_B^1 is hydrogen, halogen, hydroxyl, C_1-C_4 alkyl or $-OR^{10}$, or when B is a pyridyl, piperidyl, or pyrazolyl ring moiety, R_B^1 is hydrogen, halogen, hydroxyl, C_1-C_4 alkyl, $-OR^{10}$ or oxo. In other embodiments, R_B^1 is hydrogen, halogen, C_1-C_4 alkyl or oxo. In specific embodiments, R_B^1 is H, Br, or $-CH_3$, or, when B is a fused piperidyl ring moiety, R_B^1 is H or oxo (that is, B may be a piperidonyl fused ring moiety).

In another embodiment of this invention, R_B^2 is hydrogen, C_1-C_4 alkyl, nitro, cyano, halogen, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-NR^{10}R^{11}$, $-N(R^{11})C(O)R^{10}$, $-OC(O)NR^{10}R^{11}$, $-N(R^{11})C(O)NR^{10}R^{11}$, $-P(O)(OR^{10})_2$, $-SO_2NR^{10}R^{11}$, $-SO_3H$, or $-N(R^{11})SO_2R^{13}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl,

-SC_1-C_4 alkyl, -$NR^{11}R^{12}$, cyano, nitro, -CO_2H, -$C(O)OC_1$-C_4 alkyl, -$CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl. In other embodiments, R_B^2 is hydrogen, halogen, C_1-C_4 alkyl, -$C(O)OR^a$, -$OR^{b'}$, -NR^aR^d, -$C(O)NR^aR^d$, where said C_1-C_4 alkyl is unsubstituted or substituted with a substituent selected from of cyano, -NH_2, -CO_2H, -$CONH_2$, -CO_2C_1-C_4 alkyl, -$CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), -$CONH(C_1$-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is optionally unsubstituted or substituted with one or more of C_1-C_4 alkyl, halogen, cyano, -OH, -NH_2, and -$CONH_2$, R^a is H or methyl, $R^{b'}$ is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -NH_2, -CO_2H, -$CONH_2$, -$C(O)OC_1$-C_2 alkyl, -$CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), -$CONH(C_1$-C_4 alkyl), 5-6 membered heterocycloalkyl or heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, -NH_2, and -$CONH_2$, and R^d is H, C_1-C_2 alkyl, or phenyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl. In specific embodiments, R_B^2 is H, Cl, -OH, -OCH_3, -OCH_2CONH_2, -$OCH(CH_3)CONH_2$ or -$OCH(R$-$CH_3)CONH_2$.

In another embodiment of this invention, R_B^3 is hydrogen, halogen or C_1-C_4 alkyl or when B is a pyridyl, piperidyl, or pyrazolyl ring moiety, R_B^3 is hydrogen, halogen, C_1-C_4 alkyl or oxo. In other embodiments, R_B^3 is hydrogen, halogen or C_1-C_4 alkyl. In specific embodiments, R_B^3 is H.

In another embodiment of this invention, R_B^4 is hydrogen, halogen, C_1-C_4 alkyl, -OH or -OC_1-C_4 alkyl. In other embodiments, R_B^4 is hydrogen, halogen or C_1-C_4 alkyl. In specific embodiments, R_B^4 is H.

In another embodiment of this invention, R_{A2}^5 is hydrogen, C_1-C_4 alkyl, -$C(O)OR^{10}$, -$C(O)R^{10}$, -$C(O)NR^{10}R^{11}$, -$S(O)R^{13}$, -$S(O)_2R^{13}$, -$P(O)(OR^{10})_2$ or -$SO_2NR^{10}R^{11}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -$NR^{11}R^{12}$, cyano, -CO_2H, -$C(O)OC_1$-C_4 alkyl, -$CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl.

In other embodiments, R_{A1}^5, R_{A3}^5 and R_{A4}^5 are each independently selected from hydrogen, C_1-C_4 alkyl, -CO_2H, -CO_2C_1-C_4 alkyl and -$C(O)C_1$-C_4 alkyl. In specific

embodiments, R_{A1}^5 and R_{A4}^5 are not present. In other specific embodiments, R_{A2}^5 is H or R_{A3}^5 is H or CH_3.

In other embodiments, R_{B1}^5, R_{B3}^5 and R_{B4}^5 are each independently selected from hydrogen, C_1-C_4 alkyl, -CO_2H, -CO_2C_1-C_4 alkyl and -$C(O)C_1$-C_4 alkyl. In specific embodiments, R_{B1}^5 and R_{B4}^5 are not present. In another embodiment, R_{B3}^5 is H or C_1-C_4 alkyl. In specific embodiments, R_{B3}^5 is CH_3.

In another embodiment of this invention, R_{B2}^5 is hydrogen, C_1-C_4 alkyl, -$C(O)OR^{10}$, -$C(O)R^{10}$, -$CONR^{10}R^{11}$, -$CON(R^{11})$phenyl, -$S(O)R^{13}$, -$S(O)_2R^{13}$, -$P(O)(OR^{10})_2$ or -$SO_2NR^{10}R^{11}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -$NR^{11}R^{12}$, cyano, -CO_2H, -$C(O)OC_1$-C_4 alkyl, -$CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl. In another embodiment, R_{B2}^5 is hydrogen, a C_1-C_4 alkyl group, -CO_2H, -$CONH_2$, -CO_2C_1-C_4 alkyl, -$CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), -$CONH(C_1$-C_4 alkyl) or -$C(O)C_1$-C_4 alkyl, where said C_1-C_4 alkyl group is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -OC_1-C_4 alkyl, -NH_2, -$NH(C_1$-C_4 alkyl), -$N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), cyano, -CO_2H, -CO_2C_1-C_4 alkyl, -$CONH_2$, -$CONH(C_1$-C_4 alkyl), -$CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), -CONH(phenyl), -$CON(C_1$-C_4 alkyl)(phenyl) and a 5-6 membered heterocycloalkyl or heteroaryl. In specific embodiments, R_{B2}^5 is H, -CH_2CH_3, -$(CH_2)_3NH_2$, -$(CH_2)_2CN$, -$(CH_2)_2CONH_2$, -CH_2CO_2H, -$CH_2CO_2CH_3$, -$(CH_2)_2$-tetrazol-5-yl, -$CONHCH_3$, -CONH(phenyl) or -$C(O)CH_3$.

In yet another embodiment of this invention, W is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_2 alkyl)-heterocycloalkyl, -(C_1-C_2 alkyl)aryl, -(C_1-C_2 alkyl)-heteroaryl, where said C_3-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, -OH, -OC_1-C_4 alkyl, -SH, -SC_1-C_4 alkyl, -$S(O)(C_1$-C_4 alkyl), -SO_3H, and -$S(O)_2(C_1$-C_4 alkyl), and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of said -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_2 alkyl)-heterocycloalkyl, -(C_1-C_2 alkyl)aryl, -(C_1-C_2 alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, cyano, nitro, -OH, -NH_2, -OC_1-C_4 alkyl, -$N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), and -$NH(C_1$-C_4 alkyl). In other embodiments, W is C_4-C_6 alkyl, C_4 alkenyl, C_4 alkynyl, -(C_1-C_2 alkyl)-(C_3-C_6 cycloalkyl), -(C_1 alkyl)-heterocycloalkyl, -(C_1 alkyl)-aryl, or -(C_1 alkyl)-heteroaryl, where the

C_4-C_6 alkyl, C_4 alkenyl or C_4 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, $-OCH_3$, $-SCH_3$, and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of the -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_4 alkyl)-heterocycloalkyl, -(C_1-C_4 alkyl)-heterocycloalkyl, -(C_1-C_4 alkyl)-aryl, or -(C_1-C_4 alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from $-CH_3$, halogen, nitro, cyano, $-OR^a$, $-NR^aR^a$, where , each R^a is independently H or methyl. In specific embodiments, W is $-(CH_2)_2CH(CH_3)_2$, $-(CH_2)_2C(CH_3)_3$, $-(CH_2)_2CH(CH_3)CH_2CH_3$, $-(CH_2)_2$(cyclopropyl) or $-CH_2$(3-tetrahydrofuryl).

In any of the above embodiments, each R^{10} may be independently selected from the group consisting of hydrogen and C_1-C_4 alkyl, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, $-NR^{11}R^{12}$, cyano, nitro, $-CO_2H$, $-CO_2C_1$-C_4 alkyl, $-CONR^{11}R^{12}$, $-NR^{11}CONR^{11}R^{12}$, $-OCONR^{11}R^{12}$, $-SO_2NR^{11}R^{12}$, $-COR^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl.

In any of the above embodiments, each R^{11} may be independently hydrogen or C_1-C_4 alkyl.

In any of the above embodiments, each R^{12} may be independently hydrogen, C_1-C_4 alkyl, or monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl.

In any of the above embodiments, each R^{13} may be independently a C_1-C_4 alkyl group, which is optionally unsubstituted or substituted with one or more substituents independently selected from halogen, $-OR^{14}$, $-NR^{11}R^{14}$, cyano, nitro, $-CO_2R^{14}$, $-CONR^{11}R^{14}$, $-NR^{11}CONR^{11}R^{14}$, $-OCONR^{11}R^{14}$, $-SO_2NR^{11}R^{14}$, and $-COR^{14}$.

In any of the above embodiments, each R^{14} may be independently hydrogen or C_1-C_4 alkyl.

Specific examples of the compounds of this invention comprise compounds of Formula I, wherein:

A is a substituted or unsubstituted phenyl, pyridyl, pyrazolyl or thienyl ring moiety, wherein when n is 0, A^1 is CH or S, A^2 is $CR_A{}^2$, N, and A^3 is CH, NH, N-C_1-C_4 alkyl or S; or when n is 1, A^1 is CH, A^2 is $CR_A{}^2$, A^3 is CH, and A^4 is CH or N;

B is a substituted or unsubstituted phenyl, pyridyl, piperidyl, pyrazolyl or thienyl ring moiety, wherein when n is 0, B^1 is $CR_B{}^1$, B^2 is N or $CR_B{}^2$, and B^3 is N, N-C_1-C_4 alkyl or S; or when n is 1: B^1 is CH, CH_2 or C=O; B^2 is $CR_B{}^2$, N, N→O or $NR_{B2}{}^5$, B^3 is CH, CH_2 or $CH(CH_3)$ and B^4 is CH, CH_2 or N;

wherein A and B are not both phenyl.

One preferred embodiment of this invention relates to a compound of Formula (I) wherein A is a substituted or unsubstituted phenyl, pyridyl, or thienyl ring moiety, wherein when n is 0, A^1 is CH or S, A^2 is CR_A^2, and A^3 is CH or S; or when n is 1, A^1 is CH, A^2 is CR_A^2, A^3 is CH, and A^4 is CH or N;

B is a substituted or unsubstituted phenyl, pyridyl, piperidyl, or thienyl ring moiety, wherein when n is 0, B^1 is CH, B^2 is CR_B^2, and B^3 is S; or when n is 1: B^1 is CH, CH_2 or C=O; B^2 is CR_B^2, N, N→O or NR_{B2}^5, B^3 is CH or CH_2 and B^4 is CH, CH_2 or N; wherein A and B are not both phenyl and R_A^2, R_B^2 and R_{B2}^5 are as defined in any of the embodiments herein.

It is to be understood that this invention encompasses all combinations of particular, specific and/or preferred embodiments described herein.

Accordingly, one embodiment of this invention is directed to a compound of Formula I wherein:

R_A^1 is hydrogen, halogen or C_1-C_4 alkyl;

R_A^2 is hydrogen, C_1-C_4 alkyl, nitro, cyano, halogen, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-NR^{10}R^{11}$, $-N(R^{11})C(O)R^{10}$, $-OC(O)NR^{10}R^{11}$, $-N(R^{11})C(O)NR^{10}R^{11}$, $-P(O)(OR^{10})_2$, $-SO_2NR^{10}R^{11}$, $-SO_3H$, or $-N(R^{11})SO_2R^{13}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-NR^{11}R^{12}$, cyano, nitro, $-C(O)R^{10}$, $-CO_2R^{11}$, $-C(O)OC_1$-C_4 alkyl, $-CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

R_A^3 is hydrogen, halogen, C_1-C_4 alkyl or $-CO_2H$;

R_A^4 is hydrogen, halogen or C_1-C_4 alkyl;

R_B^1 is hydrogen, halogen, hydroxyl, C_1-C_4 alkyl or $-OR^{10}$, or when B is a pyridyl, piperidyl, or pyrazolyl ring moiety, R_B^1 is hydrogen, halogen, hydroxyl, C_1-C_4 alkyl, $-OR^{10}$ or oxo;

R_B^2 is hydrogen, halogen, C_1-C_4 alkyl, $-C(O)OR^a$, $-OR^{b'}$, $-NR^aR^d$, $-C(O)NR^aR^d$, where said C_1-C_4 alkyl is unsubstituted or substituted with a substituent selected from of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-CO_2C_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is optionally unsubstituted or substituted with one or more of C_1-C_4 alkyl,

halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, R^a is H or methyl, R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), 5-6 membered heterocycloalkyl or heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, and R^d is H, C_1-C_2 alkyl, or phenyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl;

$R_B{}^3$ is hydrogen, halogen or C_1-C_4 alkyl or when B is a pyridyl, piperidyl, or pyrazolyl ring moiety, $R_B{}^3$ is hydrogen, halogen, C_1-C_4 alkyl or oxo;

$R_B{}^4$ is hydrogen, halogen, C_1-C_4 alkyl, -OH or $-OC_1$-C_4 alkyl;

$R_{A1}{}^5$, $R_{A3}{}^5$ and $R_{A4}{}^5$ are each independently selected from hydrogen, C_1-C_4 alkyl, $-CO_2H$, $-CO_2C_1$-C_4 alkyl and $-C(O)C_1$-C_4 alkyl;

$R_{A2}{}^5$ is hydrogen, C_1-C_4 alkyl, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-P(O)(OR^{10})_2$ or $-SO_2NR^{10}R^{11}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-NR^{11}R^{12}$, cyano, $-CO_2H$, $-C(O)OC_1$-C_4 alkyl, $-CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

$R_{B1}{}^5$, $R_{B3}{}^5$ and $R_{B4}{}^5$ are each independently selected from hydrogen, C_1-C_4 alkyl, $-CO_2H$, $-CO_2C_1$-C_4 alkyl and $-C(O)C_1$-C_4 alkyl;

$R_{B2}{}^5$ is hydrogen, C_1-C_4 alkyl, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-CONR^{10}R^{11}$, $-CON(R^{11})$phenyl, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-P(O)(OR^{10})_2$ or $-SO_2NR^{10}R^{11}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-NR^{11}R^{12}$, cyano, $-CO_2H$, $-C(O)OC_1$-C_4 alkyl, $-CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

W is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(C_1$-C_4 alkyl)-(C_3-C_6 cycloalkyl), $-(C_1$-C_2 alkyl)-heterocycloalkyl, $-(C_1$-C_2 alkyl)aryl, $-(C_1$-C_2 alkyl)-heteroaryl, where said C_3-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, -OH, $-OC_1$-C_4 alkyl, -SH, $-SC_1$-C_4 alkyl, $-S(O)(C_1$-C_4 alkyl), $-SO_3H$, and $-S(O)_2(C_1$-C_4 alkyl), and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of said

-(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_2 alkyl)-heterocycloalkyl, -(C_1-C_2 alkyl)aryl, -(C_1-C_2 alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, cyano, nitro, -OH, -NH_2, -OC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -NH(C_1-C_4 alkyl);

each R^{10} may be independently selected from the group consisting of hydrogen and C_1-C_4 alkyl, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -$NR^{11}R^{12}$, cyano, nitro, -CO_2H, -CO_2C_1-C_4 alkyl, -$CONR^{11}R^{12}$, -$NR^{11}CONR^{11}R^{12}$, -$OCONR^{11}R^{12}$, -$SO_2NR^{11}R^{12}$, -COR^{12}, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

each R^{11} may be independently hydrogen or C_1-C_4 alkyl;

each R^{12} may be independently hydrogen, C_1-C_4 alkyl, or monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

each R^{13} may be independently a C_1-C_4 alkyl group, which is optionally unsubstituted or substituted with one or more substituents independently selected from halogen, -OR^{14}, -$NR^{11}R^{14}$, cyano, nitro, -CO_2R^{14}, -$CONR^{11}R^{14}$, -$NR^{11}CONR^{11}R^{14}$, -$OCONR^{11}R^{14}$, -$SO_2NR^{11}R^{14}$, and -COR^{14};

each R^{14} may be independently hydrogen or C_1-C_4 alkyl.

Another embodiment of this invention is directed to a compound of Formula I wherein: R_A^1 is hydrogen or halogen;

R_A^2 is hydrogen, halogen, -OR^b or -NHR^b, where R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -OH, -CO_2H, -$CONH_2$, -C(O)OC_1-C_2 alkyl, -CONH(C_1-C_2 alkyl) and 5-6 membered heterocycloalkyl or heteroaryl;

R_A^3 is H, halogen, or C_1-C_4 alkyl;

R_A^4 is hydrogen;

R_B^1 is hydrogen, halogen, C_1-C_4 alkyl or oxo;

R_B^2 is hydrogen, halogen, C_1-C_4 alkyl, -C(O)OR^a, -$OR^{b'}$, -NR^aR^d, -C(O)NR^aR^d, where said C_1-C_4 alkyl is unsubstituted or substituted with a substituent selected from of cyano, -NH_2, -CO_2H, -$CONH_2$, -CO_2C_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is optionally unsubstituted or substituted with one or more of C_1-C_4 alkyl, halogen, cyano, -OH, -NH_2, and -$CONH_2$, R^a is H or methyl, $R^{b'}$ is H or C_1-C_4 alkyl, where

the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CON(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), 5-6 membered heterocycloalkyl or heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH; $-NH_2$, and $-CONH_2$, and R^d is H, C_1-C_2 alkyl, or phenyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl;

$R_B{}^3$ is hydrogen, halogen or C_1-C_4 alkyl;

$R_B{}^4$ is hydrogen, halogen or C_1-C_4 alkyl;

$R_{A1}{}^5$, $R_{A2}{}^5$, $R_{A3}{}^5$ and $R_{A4}{}^5$ are each independently selected from hydrogen, C_1-C_4 alkyl, $-CO_2H$, $-CO_2C_1$-C_4 alkyl and $-C(O)C_1$-C_4 alkyl;

$R_{B1}{}^5$, $R_{B3}{}^5$ and $R_{B4}{}^5$ are each independently selected from hydrogen, C_1-C_4 alkyl, $-CO_2H$, $-CO_2C_1$-C_4 alkyl and $-C(O)C_1$-C_4 alkyl;

$R_{B2}{}^5$ is hydrogen, a C_1-C_4 alkyl group, $-CO_2H$, $-CONH_2$, $-CO_2C_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl) or $-C(O)C_1$-C_4 alkyl, where said C_1-C_4 alkyl group is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, $-OC_1$-C_4 alkyl, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), cyano, $-CO_2H$, $-CO_2C_1$-C_4 alkyl, $-CONH_2$, $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), -CONH(phenyl), $-CON(C_1$-C_4 alkyl)(phenyl) and a 5-6 membered heterocycloalkyl or heteroaryl;

W is C_4-C_6 alkyl, C_4 alkenyl, C_4 alkynyl, $-(C_1$-C_2 alkyl$)$-$(C_3$-C_6 cycloalkyl), $-(C_1$ alkyl$)$-heterocycloalkyl, $-(C_1$ alkyl$)$-aryl, or $-(C_1$ alkyl$)$-heteroaryl, where the C_4-C_6 alkyl, C_4 alkenyl or C_4 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, $-OCH_3$, $-SCH_3$, and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of the $-(C_1$-C_4 alkyl$)$-$(C_3$-C_6 cycloalkyl), $-(C_1$-C_4 alkyl$)$-heterocycloalkyl, $-(C_1$-C_4 alkyl$)$-heterocycloalkyl, $-(C_1$-C_4 alkyl$)$-aryl, or $-(C_1$-C_4 alkyl$)$-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from $-CH_3$, halogen, nitro, cyano, $-OR^a$, $-NR^aR^a$, where , each R^a is independently H or methyl.

Another embodiment of this invention is directed to a compound of Formula I wherein:

$R_A{}^1$ is hydrogen or halogen;

R_A^2 is hydrogen, halogen, $-OR^b$ or $-NHR^b$, where R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -OH, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CONH(C_1$-C_2 alkyl), and unsubstituted monocyclic heteroaryl;

R_A^3 is H, halogen, or C_1-C_4 alkyl;

R_A^4 is hydrogen;

R_{A1}^5, R_{A2}^5, R_{A3}^5 and R_{A4}^5 are each independently selected from hydrogen, C_1-C_4 alkyl, $-CO_2H$, $-CO_2C_1$-C_4 alkyl and $-C(O)C_1$-C_4 alkyl;

R_B^1 is hydrogen, halogen, C_1-C_4 alkyl, $-OR^{b1}$ or oxo, where R^{b1} is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), and $-CONH(C_1$-C_4 alkyl);

R_B^2 is hydrogen, halogen, C_1-C_4 alkyl, $-C(O)OR^a$, $-OR^{b'}$, $-NR^aR^d$, $-C(O)NR^aR^d$, where said C_1-C_4 alkyl is unsubstituted or substituted with a substituent selected from of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-CO_2C_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is optionally unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, R^a is H or methyl, $R^{b'}$ is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, and R^d is H, C_1-C_2 alkyl, or phenyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl;

R_B^3 is hydrogen, halogen or C_1-C_4 alkyl;

R_B^4 is hydrogen, halogen or C_1-C_4 alkyl;

R_{B1}^5, R_{B3}^5 and R_{B4}^5 are each independently selected from hydrogen, C_1-C_4 alkyl, $-CO_2H$, $-CO_2C_1$-C_4 alkyl and $-C(O)C_1$-C_4 alkyl;

R_{B2}^5 is hydrogen, a C_1-C_4 alkyl group, $-CO_2H$, $-CONH_2$, $-CO_2C_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-CONH(C_1$-C_4 alkyl) or $-C(O)C_1$-C_4 alkyl, where said

C_1-C_4 alkyl group is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -OC_1-C_4 alkyl, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), cyano, -CO_2H, -CO_2C_1-C_4 alkyl, -$CONH_2$, -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(phenyl), -CON(C_1-C_4 alkyl)(phenyl) and a monocyclic heteroaryl;

W is C_4-C_6 alkyl, C_4 alkenyl, C_4 alkynyl, -(C_1-C_2 alkyl)-(C_3-C_6 cycloalkyl), -(C_1 alkyl)-heterocycloalkyl, -(C_1 alkyl)-aryl, or -(C_1 alkyl)-heteroaryl, where the C_4-C_6 alkyl, C_4 alkenyl or C_4 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -OCH_3, -SCH_3, and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of the -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_4 alkyl)-heterocycloalkyl, -(C_1-C_4 alkyl)-heterocycloalkyl, -(C_1-C_4 alkyl)-aryl, or -(C_1-C_4 alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from -CH_3, halogen, nitro, cyano, -OR^a, -NR^aR^a, where , R^a is independently H or methyl;

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, embodiment of this invention is directed to a compound of Formula I wherein:

$R_A{}^1$, $R_A{}^3$ and $R_A{}^4$ are each H;

$R_A{}^2$ is H, Br, F, -OH or -OCH_2CN;

$R_{A1}{}^5$ and $R_{A4}{}^5$ are not present;

$R_{A2}{}^5$ is H or $R_{A3}{}^5$ is H or CH_3;

$R_B{}^1$ is H, Br, or -CH_3, or, when B is a fused piperidyl ring moiety, $R_B{}^1$ is H or oxo;

$R_B{}^2$ is H, Cl, -OH, -OCH_3, -OCH_2CONH_2, -$OCH(CH_3)CONH_2$ or -$OCH(R\text{-}CH_3)CONH_2$;

$R_B{}^3$ and $R_B{}^4$ are each H;

$R_{B1}{}^5$ and $R_{B4}{}^5$ are not present;

$R_{B2}{}^5$ is H, -CH_2CH_3, -$(CH_2)_3NH_2$, -$(CH_2)_2CN$, -$(CH_2)_2CONH_2$, -CH_2CO_2H, -$CH_2CO_2CH_3$, -$(CH_2)_2$-tetrazol-5-yl, -$CONHCH_3$, -CONH(phenyl) or -$C(O)CH_3$;

$R_{B3}{}^5$ is CH_3;

W is -$(CH_2)_2CH(CH_3)_2$, -$(CH_2)_2C(CH_3)_3$, -$(CH_2)_2CH(CH_3)CH_2CH_3$, -$(CH_2)_2$(cyclopropyl) or -CH_2(3-tetrahydrofuryl);

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

If a substituent described herein is not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Chemical Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

In the compounds of this invention, various substituents may be a "protected -OH" group. This term refers to a substituent represented as $-OR^P$, where R^P refers to a suitable protecting group for an -OH moiety. Hydroxyl protecting groups are well known in the art and any hydroxyl protecting group that is useful in the methods of preparing the compounds of this invention may be used. Exemplary hydroxyl protecting groups include benzyl, tetrahydropyranyl, silyl (trialkyl-silyl, diaryl-alkyl-silyl, etc.) and various carbonyl-containing protecting groups, as disclosed in T. Greene and P. Wuts, *supra*. For example, in the compounds of this invention, R_A^2 may be the protected hydroxyl moiety -OSi(*tert*-butyl)$(CH_3)_2$.

The compounds of this invention may contain at least one chiral center and may exist as single stereoisomers (e.g., single enantiomers), mixtures of stereoisomers (e.g. any mixture or enantiomers or diastereomers) or racemic mixtures thereof. All such single stereoisomers, mixtures and racemates are intended to be encompassed within the broad scope of the present invention. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that are at least 90% enantiomerically pure. Where the stereochemistry of the chiral carbons present in the chemical structures illustrated herein is not specified, the chemical structure is intended to encompass compounds containing either stereoisomer of each chiral center present in the compound. Such compounds may be obtained synthetically, according to the procedures described herein using optically pure (enantiomerically pure) or substantially optically pure

materials. Alternatively, these compounds may be obtained by resolution/separation of a mixture of stereoisomers, including racemic mixtures, using conventional procedures. Exemplary methods that may be useful for the resolution/separation of mixtures of stereoisomers include chromatography and crystallization/re-crystallization. Other useful methods may be found in "*Enantiomers, Racemates, and Resolutions,* " J. Jacques et al., 1981, John Wiley and Sons, New York, NY, the disclosure of which is incorporated herein by reference.

The compounds of this invention may possess one or more unsaturated carbon-carbon double bonds. All double bond isomers, both the cis (Z) and trans (E) isomers, and mixtures thereof are intended to be encompassed within the scope of the present invention.

The term "pharmaceutically acceptable salt" is intended to describe a salt that retains the biological effectiveness of the free acid or base of a specified compound and is not biologically or otherwise undesirable.

If an inventive compound is a base, a desired salt may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid or the like. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, phenylacetates, phenylpropionates, phenylbutrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates mandelates, and sulfonates, such as xylenesulfonates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates and naphthalene-2-sulfonates.

If an inventive compound is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic

base, such as an amine (primary, secondary, or tertiary), an alkali metal or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as ethylene diamine, dicyclohexylamine, ethanolamine, piperidine, morpholine, and piperazine, as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium. Particular pharmaceutically acceptable salts of a compound of Formula I include the sodium salt and the potassium salt.

Because the compounds of this invention may contain both acid and base moieties, pharmaceutically acceptable salts may be prepared by treating these compounds with an alkaline reagent or an acid reagent, respectively. Accordingly, this invention also provides for the conversion of one pharmaceutically acceptable salt of a compound of this invention, e.g., a hydrochloride salt, into another pharmaceutically acceptable salt of a compound of this invention, e.g., a sodium salt.

The term "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine. In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, or solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention and specified formulas.

Also included within the scope of this invention are prodrugs of the compounds of this invention. The term "prodrug" is intended to mean a compound that is converted under physiological conditions, e.g., by solvolysis or metabolically, to a compound of Formula I, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof. A prodrug may be a derivative of one of the compounds of this invention that contains, for example, a carboxylic acid ester or amide moiety or an enol-ester moiety that may be cleaved under physiological conditions. A prodrug containing such a moiety may be prepared according to conventional procedures, for example, by treatment of a compound of Formula I, containing an amino, amido or hydroxyl moiety with a suitable derivatizing agent, for example, a carboxylic acid halide or acid anhydride, or by converting a compound of Formula I, containing a carboxyl moiety to an ester or amide or by converting a compound of Formula I, containing a carboxylic acid ester moiety to an enol-ester. Prodrugs of the compounds of

this invention may be determined using techniques known in the art, for example, through metabolic studies. See, e.g., "Design of Prodrugs," (H. Bundgaard, Ed.) 1985, Elsevier Publishers B.V., Amsterdam, The Netherlands.

This invention is directed to a method of inhibiting an RNA-containing virus, which comprises contacting the virus with an effective amount of a compound of Formula I. This invention is also directed to a method of treating infection or disease caused by an RNA-containing virus comprising administering to a subject in need thereof, an effective amount of the compound of Formula I. Specifically, this invention is directed to a method of inhibiting HCV activity, comprising contacting the virus with an effective amount of a compound of Formula I, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof. For example, HCV activity may be inhibited in mammalian tissue by administering to a subject in need thereof a compound of Formula I or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

A therapeutically "effective amount" is intended to mean that amount of a compound that, when administered to a mammal in need of such treatment, is sufficient to effect treatment, as defined herein. Thus, e.g., a therapeutically effective amount of a compound of Formula I or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof is a quantity of an inventive agent that, when administered to a mammal in need thereof, is sufficient to modulate or inhibit the activity of HCV such that a disease condition which is mediated by that activity is reduced, alleviated or prevented. The amount of a given compound that will correspond to such an amount will vary depending upon factors such as the particular compound (e.g., the potency (IC_{50}), efficacy (EC_{50}), and the biological half-life of the particular compound), disease condition and its severity, the identity (e.g., age, size and weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art. Likewise, the duration of treatment and the time period of administration (time period between dosages and the timing of the dosages, e.g., before/with/after meals) of the compound will vary according to the identity of the mammal in need of treatment (e.g., weight), the particular compound and its properties (e.g., pharmaceutical characteristics), disease or condition and its severity and the specific composition and method being used, but can nevertheless be determined by one of skill in the art.

In addition, this invention is directed to a method for inhibiting replication of hepatitis C virus comprising inhibiting replication of both positive and negative strand

HCV-RNA, which method comprises contacting a cell infected with said virus with an effective amount of a compound of Formula I. This invention is also directed to a method of treating infection or disease caused by hepatitis C virus comprising inhibiting replication of both positive and negative strand HCV-RNA, which method comprises administering to a subject in need thereof, an effective amount of a compound of Formula I. More specifically, this invention is directed to a method of inhibiting replication of both positive and negative strand HCV-RNA with a compound of Formula I, wherein the compounds demonstrate substantially equal inhibition of positive strand HCV-RNA replication and negative strand HCV-RNA replication. That is, for a given compound of this invention, the IC_{50} for inhibition of positive strand HCV-RNA replication is not statistically different (less than a 2-fold difference) from the IC_{50} for inhibition of negative strand HCV-RNA replication. Generally, the compounds of this invention demonstrate an IC_{50} for inhibition of positive strand HCV-RNA replication that is $\pm$30% the IC_{50} for inhibition of negative strand HCV-RNA replication.

"Treating" or "treatment" is intended to mean at least the mitigation of a disease condition (acute, chronic, latent, etc.) in a subject (a mammal, such as a human), where the disease condition is caused by an infectious RNA-containing virus. The methods of treatment for mitigation of a disease condition include the use of the compounds in this invention in any conventionally acceptable manner, for example for prevention, retardation, prophylaxis, therapy or cure of a disease. The compounds of Formula I, Formula II and Formula III of this invention are particularly useful for the treatment of acute, chronic or latent HCV diseases, such as acute and chronic hepatitis infection, hepatocellular carcinoma, liver fibrosis, or other HCV-related diseases. The compounds of Formula I, Formula II and Formula III of this invention may also be useful for treatment of diseases caused by infectious RNA-containing viruses other than HCV, including, but not limited to, Dengue, HIV or picornaviruses. Chronic fatigue syndrome is another disease that may be treatable using the compounds of this invention.

An inventive compound of Formula I, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof may be administered to a subject as a pharmaceutical composition in any pharmaceutical form that is recognizable to the skilled artisan as being suitable. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. Pharmaceutical compositions of the invention may also include suitable

excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use or mode of administration. Administration of a compound of the Formula I, or a tautomer thereof, or pharmaceutically acceptable salt or solvate thereof, may be performed according to any of the generally accepted modes of administration available to those skilled in the art. The compounds of this invention may be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops. Alternatively, injection (e.g., parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. The compounds of the invention may also be formulated in liposome-containing preparations, particularly liposome-containing preparations useful for delivery of the compounds of this invention to the liver or potentially to nonhepatic reservoirs of infection. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories. For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

Compositions containing a compound of Formula I, or a tautomer thereof, or pharmaceutically acceptable salt or solvate thereof, which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for

preparing solid formulations may be used. Examples of such carriers include starch, calcium sulfate dihydrate, magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and may be incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula I, or a tautomer thereof, or pharmaceutically acceptable salt or solvate thereof, which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is formulated and administered in a unit dosage form. For oral application, for example, one or more tablets or capsules may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of Formula I, or a tautomer thereof, or pharmaceutically acceptable salt or solvate thereof). The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of HCV activity by any known or suitable method of administering the dose, including: topically, for example, as an ointment, or cream, orally, rectally, for

example, as a suppository, parenterally by injection, or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion.

Treatment of all forms of infection or disease (acute, chronic, latent etc) or as prophylaxis with these compounds (or their salts etc.) may be achieved using the compounds of this invention as a monotherapy, in dual or multiple combination therapy, such as in combination with other antivirals, in combination with an interferon, in combination with an interferon and ribavirin or levovirin, or in combination with one or more agents which include but are not limited to: immunomodulatory agents (such as cytokines, suppressors of cytokines and/or cytokine signalling, or immune modifiers, adjuvants and the like), immunomodulatory agents that enhance the body's immune system (such as vitamins, nutritional supplements, antioxidant compositions, vaccines or immunostimulating complexes, such as vaccines comprising a multimeric presentation of an antigen and adjuvant), other direct antiviral agents, indirect antiviral agents or agents which target viral RNA and impair translation or replication or modulate signalling or cellular host factors, or host-viral interface, immunoglobulins, antisense agents against HCV, peptide-nucleic acid conjugates, oligonucleotides, ribozymes, polynucleotides, anti-inflammatory agents, pro-inflammatory agents, antibiotics, hepatoprotectants, or any anti-infectious agents and the like, or combinations thereof. Moreover, the additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively, these additional agents may be separately administered as part of a multiple dosage form. As used herein the term "an interferon" is intended to mean any form of interferon, which includes, but is not limited to, natural or recombinant forms of alpha, beta or gamma interferons, albumin-linked interferons, or pegylated interferons.

Representative compounds of this invention include the compounds of Examples 1-47 or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

Compounds of the present invention include:

3-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-[1,8]naphthiridin-2-one,

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

1-(3,3-Dimethyl-butyl)-3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one,

(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-[1,8]napthyridin-2-one,

1-(3,3-Dimethyl-butyl)-3-(1,1-dioxo-4*H*-1,4-dihydropyrido[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one,

6-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadizine-3-yl)-7-hydroxy-4-(3-methyl-butyl)-4*H*-thieno[3,2-*b*]pyridin-5-one,

5-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadizine-3-yl)-4-hydroxy-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one,

2-Bromo-5-(1,1-dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadizine-3-yl)-4-hydroxy-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one,

3-(7-Bromo-6-Chloro-1,1-dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(6-Chloro-1,1-dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(5,7-Dimethyl-1,1-dioxo-4*H*-1,4-dihydro-5*H*-pyrazo[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(1,1-Dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(tetrahydro-furan-3-ylmethyl)-1H-quinolin-2-one,

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-pentyl)-1H-quinolin-2-one,

3-(1,1-Dioxo-1,4,5,6,7,8-hexahydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(7-Acetyl-1,1-dioxo-1,4,5,6,7,8-hexahydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1*H*-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-acetic acid methyl ester,

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-propionitrile,

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-acetic acid,

3-[7-(3-Amino-propyl)-1,1-dioxo-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

3-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-propionamide,

5-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-methyl-7-(3-methyl-butyl)-1,7-dihydro-pyrazolo[3,4-b]pyridin-6-one,

5-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-7-(3-methyl-butyl)-1,7-dihydro-pyrazolo[3,4-b]pyridin-6-one,

3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazine-7-carboxylic acid phenylamide,

3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazine-7-carboxylic acid methylamide,

3-[7-Ethyl-1,1-dioxo-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4,6-dihydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

3-[1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-6-yloxy]-acetonitrile,

3-{1,1-Dioxo-7-[2-(2H-tetrazol-5-yl)-ethyl]-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl}-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-1,7-dihydro-4H-1l6-pyrido[4,3-e][1,2,4]thiadiazin-8-one,

3-(1,1-Dioxo-7-oxy-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

1-(2-Cyclopropyl-ethyl)-3-(1,1-dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-6-flu oro-4-hydroxy-1H -quinolin-2-one,

1-(2-Cyclopropyl-ethyl)-3-(1,1-dioxo-1,4-dihydro-pyrido[2,3-e][1,2,4]thiadiazin-3-yl)-6-fluoro-4-hydroxy-1H-quinolin-2-one,

7-Hydroxy-6-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-(3-methyl-butyl)-4H-thieno[3,2-b]pyridin-5-one,

4-Hydroxy-3-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1-(3-methyl-butyl)-1H-[1,8]naphthyridin-2-one,

4-Hydroxy-3-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1-(3-methyl-butyl)-1H-[1,8]naphthyridin-2-one,

4-Hydroxy-5-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-7-(3-methyl-butyl)-7H-thieno[2,3-b]pyridin-6-one,

2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

(R)-2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

(R)-2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

2-{3-[4-Hydroxy-7-(3-methyl-butyl)-6-oxo-6,7-dihydro-thieno[2,3-b]pyridin-5-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

1-(2-Cyclopropyl-ethyl)-4-hydroxy-3-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1H-[1,8]naphthyridin-2-one,

2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin 3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide, and

(R)-2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

Preferred compounds of this invention include:

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

1-(3,3-Dimethyl-butyl)-3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one,

6-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadizine-3-yl)-7-hydroxy-4-(3-methyl-

butyl)-4*H*-thieno[3,2-*b*]pyridin-5-one,

3-(6-Chloro-1,1-dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

1-(2-Cyclopropyl-ethyl)-3-(1,1-dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-6-fluoro-4-hydroxy-1H -quinolin-2-one,

2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

(R)-2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

(R)-2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

2-{3-[4-Hydroxy-7-(3-methyl-butyl)-6-oxo-6,7-dihydro-thieno[2,3-b]pyridin-5-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin 3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide, and

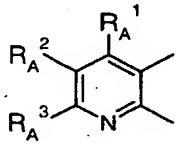
(R)-2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

Also included in the present invention are pharmaceutically acceptable salt complexes. Preferred are the ethylene diamine, sodium, potassium, calcium, ethanolamine, hydrochloride, hydrobromide, maleate and trifluoroacetate salts.

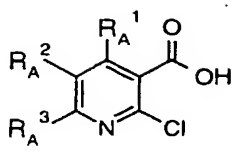
Also included in the present invention are general methods for the preparation of the compounds of Formula I, II and III of this invention, as follows.

In one embodiment, the process for the preparation of the compound of this invention, wherein the A fused ring moiety is exemplified as

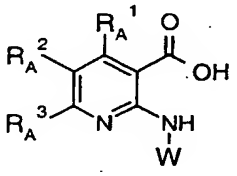


comprises

a) treating a compound having the formula:

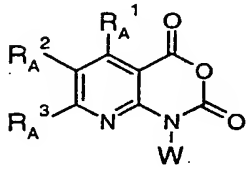


with an amine to form a compound having the formula:



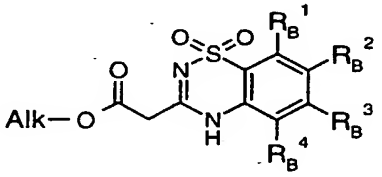
;

b) converting the compound formed in step a) into a heteroaryloxazine-2,4-dione having the formula:

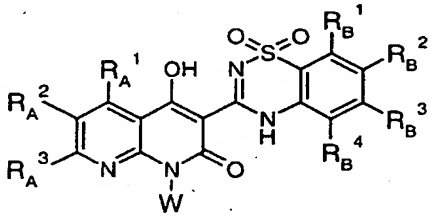


; and

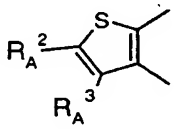
c) treating the heteroaryloxazine-2,4-dione with a substituted (1,1-dioxo-dihydrobenzo-[1,2,4]-thiadiazin-3-yl)-acetic acid alkyl ester having the formula:



to form the compound having the formula:

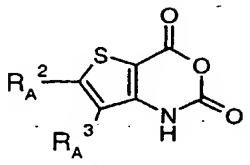


In another embodiment, the process for the preparation of the compound of this invention, wherein the A fused ring moiety is exemplified as

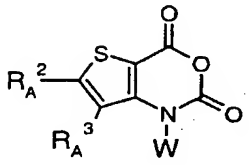


comprises

a) treating a compound having the formula:

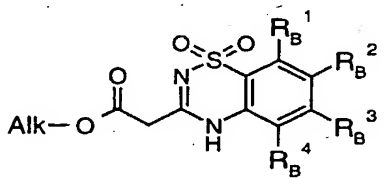


with an alkyl halide or an alkanol to form a heteroaryloxazine-2,4-dione having the formula:

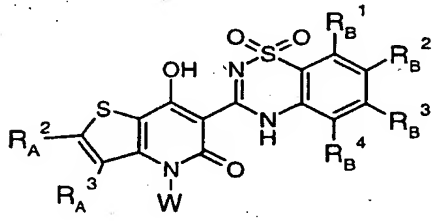


; and

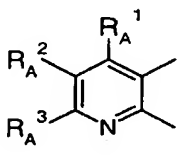
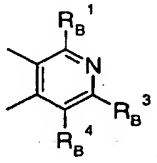
b) treating the heteroaryloxazine-2,4-dione with a substituted (1,1-dioxo-dihydrobenzo-[1,2,4]-thiadiazin-3-yl)-acetic acid alkyl ester having the formula:



to the compound having the formula:

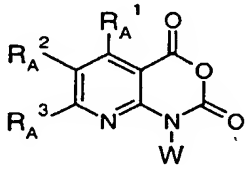


In yet another embodiment, the process for the preparation of the compound of this invention, wherein the A and B fused ring moieties are exemplified as

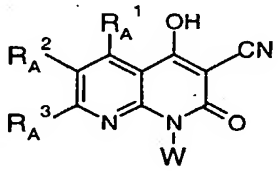
 and:  , respectively,

comprises

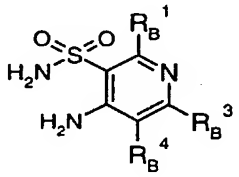
a) converting a compound having the formula:



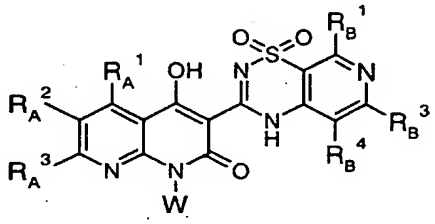
into a compound having the formula:

 ; and

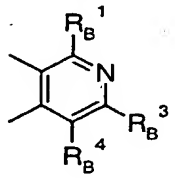
b) treating the compound formed in step a) with an ortho-amino-heteroaryl sulfonic acid amide having the formula:



to form a compound having the formula:

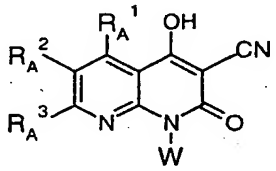


In yet another embodiment, the process for the preparation of the compound of this invention, wherein the B fused ring moiety is exemplified as

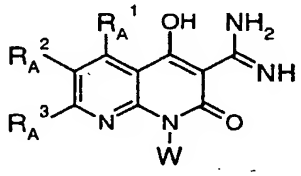


comprises

a) converting a compound having the formula:

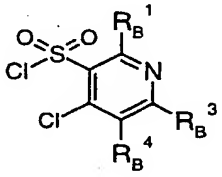


into an amidine compound having the formula

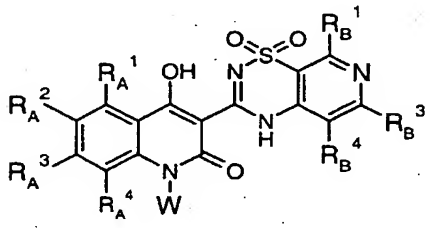


; and

b) treating the amidine compound formed in step a) with an ortho-chloro-heteroarylsulfonyl chloride having the formula:

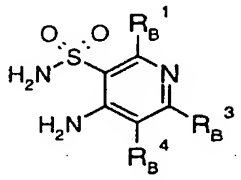


to form a compound having the formula:

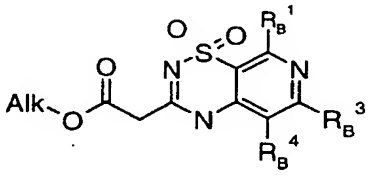


Another process for the preparation of the above compounds comprises

a) treating a compound having the formula:

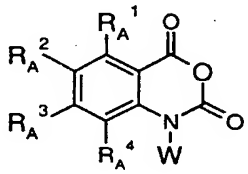


with a 3,3,3-trialkoxy-propionic acid alkyl ester to form a compound having the formula

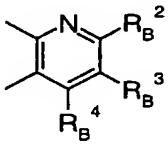


; and

b) treating the compound formed in step a) with an aryloxazine-2,4-dione having the formula:

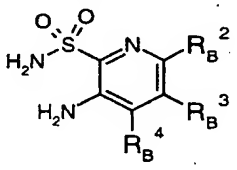


In another embodiment, the process for the preparation of the compound of this invention, wherein the B fused ring moiety is exemplified as

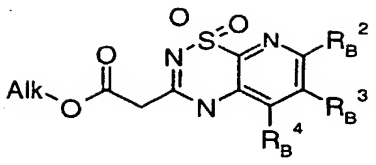


comprises

a) treating a compound having the formula:

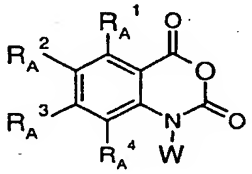


with a 3,3,3-trialkoxy-propionic acid alkyl ester to form the compound having the formula

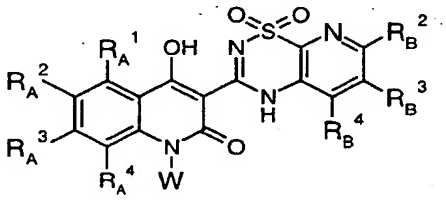


; and

b) treating the compound formed in step a) with an aryloxazine-2,4-dione having the formula:

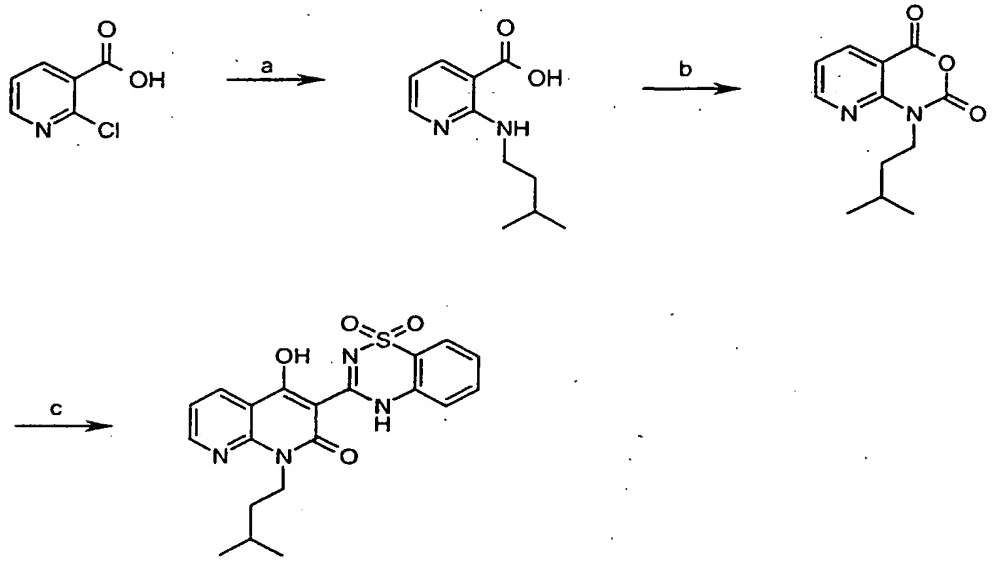


to form a compound having the formula:



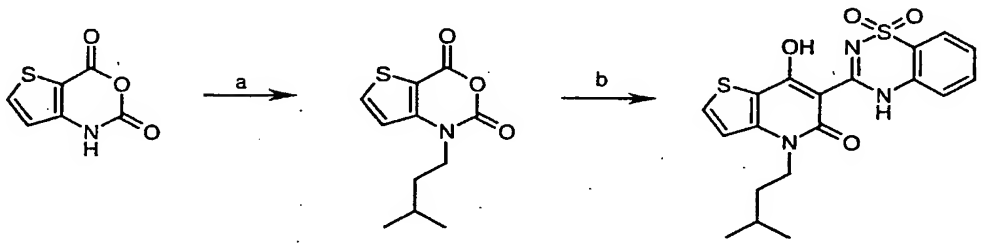
Also included in the present invention is a process according to Scheme 1 for the synthesis of the compounds:

SCHEME 1



Preparation of the compounds of this invention may be achieved via reaction of a heteroaryloxazine-2,4-dione with a substituted (1,1-dioxo-dihydrobenzo-[1,2,4]-thiadiazin-3-yl)-acetic acid alkyl ester (step (c)). The heteroaryloxazine-2,4-dione intermediate may be prepared from a heteroarylcarboxylic acid. Conditions: a) 1] K_2CO_3, H_2O; 2] 3-methyl-butylamine, copper(0), DMF, reflux; b) Na_2CO_3, H_2O, $COCl_2$ (20% in toluene); c) 1] (1,1-Dioxo-*4H*-1,4-dihydrobenzo-[1,2,4]-thiadiazin-3-yl)-acetic acid ethyl ester, NaH, THF, reflux; 2] acetic acid, reflux.

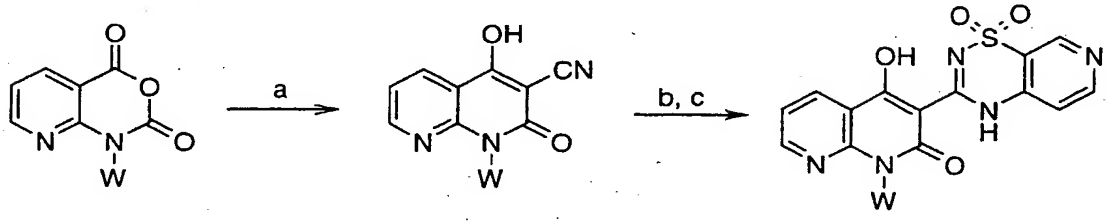
SCHEME 2



Preparation of the compounds of this invention may be achieved via reaction of a heteroaryloxazine-2,4-dione with a substituted (1,1-dioxo-dihydrobenzo-[1,2,4]-thiadiazin-3-yl)-acetic acid alkyl ester. Conditions: a) 1] NaH, DMA; 2]1-bromo-3-methylbutane; b)

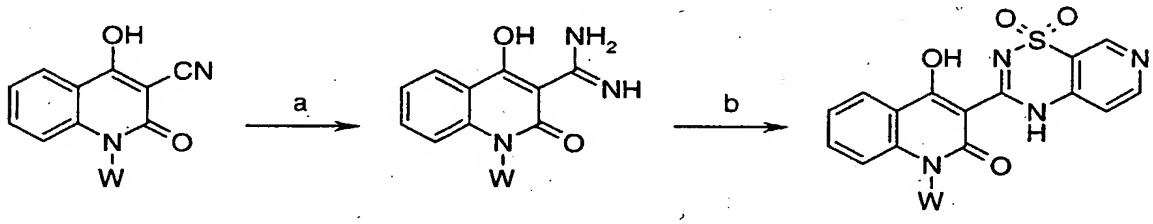
1] (1,1-Dioxo-4*H*-1,4-dihydrobenzo-[1,2,4]-thiadiazin-3-yl)-acetic acid ethyl ester, NaH, THF, reflux; 2] acetic acid, reflux

SCHEME 3



Preparation of the compounds of this invention may be achieved via condensation of a substituted 4-hydroxy-1-alkyl-1,2-dihydro-quinolin-2-one-3-carbonitrile with an ortho-amino-heteroaryl sulfonic acid amide. Conditions: a) sodium hydride, methyl cyanoacetate, DMF; b) 4-amino-pyridine-3-sulfonic acid amide, Me_3Al, 1,4-dioxane; c) sodium hydroxide / reflux.

SCHEME 4



Preparation of the compounds of this invention may be achieved via condensation of a 4-hydroxy-1-alkyl-1,2-dihydro-quinolin-2-one-3-carboxamidine with an ortho-chloro-heteroarylsulfonyl chloride. Conditions: a) NH_4Cl, Me_3Al, 1,4-dioxane, reflux; b) 4-chloropyridine-3-sulfonyl chloride, NaH, THF or DMF, reflux

If a substituent described herein is not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Chemical Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which

is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

In the compounds of this invention, various substituents may be a "protected -OH" group. This term refers to a substituent represented as $-OR^P$, where R^P refers to a suitable protecting group for an -OH moiety. Hydroxyl protecting groups are well known in the art and any hydroxyl protecting group that is useful in the methods of preparing the compounds of this invention may be used. Exemplary hydroxyl protecting groups include alkyl, benzyl, tetrahydropyranyl, silyl (trialkyl-silyl, diaryl-alkyl-silyl, etc.), carbonyl-containing protecting groups, as disclosed in T. Greene and P. Wuts, *supra*. For example, in the compounds of this invention, R_A^2 or R_B^2 may be the protected hydroxyl moiety $-OSi(R^{10})(R^{10})(R^{10})$, wherein R^{10} is defined as above.

With appropriate manipulation and protection of chemical functionality, synthesis of the compounds of Formula (I) may be accomplished by methods analogous to those described above and in the following Examples.

Also included within the scope of the present invention are intermediate compounds that are useful for the preparation of the compounds of Formula I. Such useful intermediate compounds include: 2-(3-methyl-butylamino)-nicotinic acid, 1-(3-methyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione, 2-(-3,3-dimethyl-butylamino)-nicotinic acid, 1-(3,3-dimethyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione, 1-(3,3-dimethyl-butyl)-4-hydroxy-2-oxo-1,2-dyhydro-[1,8]napthyridine-carbonitrile, 1-(3,3-dimethyl-butyl)-4-hydroxy-2-oxo-1,2-dyhydro-[1,8]napthyridine-carboxamidine, 1-(3-methyl-butyl)-1H-thieno[3,2-d][1,3]oxazine-2,4-dione, 1-(3-Methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione, 6-bromo-1-(3-methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione, 4-hydroxy-2-oxo-1-(tetrahydro-furan-3-ylmethyl)-1,2-dihydro-quinoline-3-carbonitrile, 4-hydroxy-2-oxo-1-(tetrahydro-furan-3-ylmethyl)-1,2-dihydro-quinoline-3-carboxamidine, 4-hydroxy-1-(3-methyl-pentyl)-2-oxo-1,2-dihydro-quinoline-3-carbonitrile, 4-hydroxy-1-(3-methyl-pentyl)-2-oxo-1,2-dihydro-quinoline-3-carboxamidine, (1,1-dioxo-1,4-dihydro-1-thia-2,4,8-triaza-naphthalen-3-yl)-acetic acid ethyl ester, ethyl 1-methyl-5-(3-methyl-butylamino)-1*H*-pyrazole-4-carboxylate, (1,1-dioxo-1,4-dihydro-1-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-acetic acid ethyl ester, 1-(2-cyclopropyl-ethyl)-6-fluoro-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-

carbonitrile, 1-(2-cyclopropyl-ethyl)-6-fluoro-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxamidine, 7-hydroxy-6-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-(3-methyl-butyl)-4*H*-thieno[3,2-*b*]pyridin-5-one, 4-hydroxy-5-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one, 2-(2-cyclopropyl-ethyl)-nicotinic acid, 1-(2-cyclopropyl-ethyl)-1*H*-pyrido[2,3-*d*][1,3]-oxazine-2,4-dione, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

The activity of the inventive compounds as inhibitors of HCV activity may be measured by any of the suitable methods known to those skilled in the art, including *in vivo* and *in vitro* assays. For example, the HCV NS5B inhibitory activity of the compounds of Formula I as determined using standard assay procedures described in Behrens et al., EMBO J. 15:12-22 (1996), Lohmann et al., Virology 249:108-118 (1998) and Ranjith-Kumar et al., J. Virology 75:8615-8623 (2001). Unless otherwise noted, the compounds of this invention have demonstrated *in vitro* HCV NS5B inhibitory activity in such standard assays and have IC_{50}'s in the range of 0.0001 μM to 100 μM. Representative compounds of Formula I, for example the compounds of Examples 34-36 and 38-41. have demonstrated *in vitro* HCV NS5B inhibitory activity and have IC_{50}'s in the range of 0.0005 μM to 5 μM. Recently, cell-based replicon systems for HCV have been developed, in which the nonstructural proteins stably replicate subgenomic viral RNA in Huh7 cells (Lohmann et al., Science (1999) and Blight et al., Science (2000). In the absence of a purified, functional HCV replicase consisting of viral non-structural and host proteins, our understanding of *Flaviviridae* RNA synthesis comes from studies using active recombinant RdRps and validation of these studies in the HCV replicon system. Inhibition of recombinant purified HCV polymerase with compounds in *in vitro* biochemical assays may be validated using the replicon system whereby the polymerase exists within a replicase complex, associated with other viral and cellular polypeptides in appropriate stoichiometry. Demonstration of cell-based inhibition of HCV replication may be more predictive of *in vivo* function than demonstration of HCV NS5B inhibitory activity in *in vitro* biochemical assays.

Advantageously, the compounds of this invention inhibit both positive and negative strand HCV-RNA replication. The following methods have been developed and used for determining the positive and negative strand HCV-RNA replication inhibition activity of the compounds of this invention.

Test Method 1

Method for positive strand replicon HCV-RNA detection in replicon cells

Replicon cells were plated at 3 X 10^3 cells per well in a 96-well plate plates at 37° and 5% CO_2 in DMEM (Dulbecco's Minimal Essential Medium) containing 10% FCS (fetal calf serum), 1% NEAA (nonessential amino acids) and 1 mg/ml Geneticin (G418 neomycin). After allowing 4 h for cell attachment, 1 µl of a solution of candidate antiviral agent was added to the medium (n = 8 wells per dilution). Briefly, eleven 2.5-fold dilutions of 1 mM stock test compound in DMSO (dimethylsulfoxide) were prepared with final concentration ranging from 10000 nM to 1.0 nM. Plates were incubated for 40 h, until reaching 80% confluence. After removal of medium, 150 µl Buffer RLT (Qiagen, Valencia, California, US) was added to each well and RNA purified according to manufacturer's recommendations (Qiagen RNAeasy) and were eluted twice in 45 µl dH_2O prior to RT-PCR. Approximately 40 µl of TaqMan EZ RT-PCR (Applied Biosystems, Foster City, California, US) master mix (1X TaqMan EZ Buffer, 3 mM $Mn(OAc)_2$, 0.3 mM dATP, 0.3 mM dCTP, 0.3 mM dGTP, 0.6 mM dUTP, 0.2 mM neo-forward, 0.2 mM neo-reverse, 0.1 mM neo-probe, 1X Cyclophilin Mix, 0.1 Unit/µl r*Tth* DNA Polymerase, 0.01 Unit/µl AmpErase UNG, and H_2O to 40 µl) was added to each tube of 96-tube optical plate along with 10 µl of RNA elution. Primers and probes specific for the positive strand RNA detection of neomycin gene were: neo-forward: 5'CCGGCTACCTGCCCATTC3' (SEQ ID NO 1); neo-reverse: 5'CCAGATCATCCTGATCGACAAG3' (SEQ ID NO 2); neo-probe: 5'FAM-ACATCGCATCGAGCGAGCACGTAC-TAMRA3' (SEQ ID NO 3). For negative strand RNA detection, the cDNA primer used was 5'ACA TGC GCG GCA TCT AGA CCG GCT ACC TGC CCA TTC3' (SEQ ID NO 4) whereby the first 18 bases represent SEQ ID NO 5 linked to neo sequences; neo-forward tag: 5'ACA TGC GCG GCA TCT AGA3' (SEQ ID NO 5); neo reverse 5'CCAGATCATCCTGATCGACAAG3' (SEQ ID NO 6); neo probe: 5'FAM-ACA TCG CAT CGA GCG AGC ACG TAC-TAMRA3' (SEQ ID NO 3). Additionally, the PDAR control reagent human cyclophilin was used for normalization. Samples were mixed briefly and placed in an ABI7700 (Applied Biosystems) at 50°C, 2 min; 60°C, 30 min; and 95°C, 5 min, with cycling parameters set to 94°C, 20 s; 55°C, 1 min for 40 cycles. The relative cDNA levels for neo and cyclophilin were determined compared to DMSO-only treated controls and the ratio of neo:cyclophilin was used for IC_{50} calculation (n = 8).

Test Method 2

Method for negative strand replicon HCV-RNA detection in replicon cells

To achieve strand-specific detection, a primer containing HCV RNA (or replicon RNA sequences such as neomycin gene) and an 18 base tag of nonrelated sequence at the 5' end was for the reverse transcription (RT) reaction, 5'ACATGCGCGGCATCTAGACCGGCTACCTGCCCATTC3' (SEQ ID NO 4). A Thermoscript-RT-PCR system (Invitrogen) was used for the RT reaction according to the manufacturer's protocol, with approximately 9 µl of the cell-harvested RNA and 1 µl of primer (10 µM) incubated with RT at 60°C for 1 h. Following that incubation, 2 µl of cDNA product containing the 5' tag was amplified for TaqMan quantification using the 48 µl of TaqMan Universal Master Mix (Applied Biosystems) as well as primers, neo-forward tag: 5'ACA TGC GCG GCA TCT AGA3' (SEQ ID NO 5); neo reverse: 5'CCAGATCATCCTGATCGACAAG3' (SEQ ID NO 6); and neo probe: 5'FAM-ACA TCG CAT CGA GCG AGC ACG TAC-TAMRA3' (SEQ ID NO 3). Samples were mixed briefly and placed in an ABI7700 (Applied Biosystems) at 50°C, 2 min; 95°C, 10 min, with cycling parameters set to 94°C, 15 s; 55°C, 1 min for 40 cycles. The negative strand copy number in each reaction was determined using linear regression analysis based on the slope and intercept generated with a negative strand copy standard curve. The negative strand copies per cell were determined by dividing the total negative strand copies per reaction by the total cells per reaction.

Through routine experimentation, including appropriate manipulation and protection of any chemical functionality, synthesis of the compounds of Formula I is accomplished by methods analogous to those above and to those described in the following Experimental section.

Example 1

3-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]-thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-[1,8]-naphthyridin-2-one

a) 2-(3-Methyl-butylamino)-nicotinic acid

To a stirred solution of potassium carbonate (2.1 eq, 66.0 mmol, 9.1g) in water (40 mL) was added 2-chloronicotinic acid (5.0g, 31.7 mmol). After a few minutes, the solution becomes homogeneous and the water was removed in vacuo. 3-Methyl-butylamine (1.6 eq, 50.1 mmol, 4.4g) was added, followed by copper powder (2.1 eq, 66.0 mmol, 4.2g) and anhydrous dimethylformamide (75 mL). The mixture was heated to reflux, stirring at this

temperature overnight. It was cooled to room temperature and concentrated. A solution of sodium hydroxide in water was added, and the resulting copper precipitate was filtered off. The filtrate was acidified to pH 7 using 3N HCl, and the cloudy light green mixture was allowed to stand for one hour. The product, which precipitated as a light blue solid, was filtered, washed with water and ethanol/diethyl ether, and dried (2.5g, 38%).

b) 1-(3-Methyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione

To a solution of sodium carbonate (3.5 eq, 40.3 mmol, 4.3g) in water (80 mL) was added 2-(3-methyl-butylamino)-nicotinic acid, and the mixture was stirred vigorously for ten minutes. Phosgene (2.7 eq, 31.1 mmol, 16.0 mL of a 20% solution in toluene) was then added, and the mixture was allowed to stir vigorously overnight under nitrogen. Solid sodium carbonate was added until the mixture reached pH 9. Water was added and the resulting blue solid was filtered off. The filtrate was extracted with ethyl acetate, washing with water and saturated sodium chloride. The combined organic portions were dried over Na_2SO_4, filtered, and concentrated to provide the product (1.1g, 41%) as a pale yellow solid.

c) 3-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]-thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-[1,8]-naphthyridin-2-one

1-(3-Methyl-butyl)-1*H*-pyrido[*2,3-d*][1,3]-oxazine-2,4-dione (0.60g, 2.6 mmol) was suspended in freshly distilled tetrahydrofuran (21 mL). (1,1-Dioxo-1,4-dihydro-benzo-[1,2,4]-thiadiazin-3-yl)-acetic acid ethyl ester (1.0 eq, 2.6 mmol, 0.69g) was added, followed by sodium hydride (4.0 eq, 10.2 mmol, 0.41g of a 60% dispersion in mineral oil). The yellow suspension was heated to reflux and allowed to stir at this temperature for one hour. After cooling to room temperature, acetic acid was carefully added until the bubbling subsided. The now homogeneous solution was refluxed for an additional hour. It was cooled to room temperature and poured into 1N HCl. The yellow solid was filtered off and triturated with diethyl ether to remove all traces of mineral oil. The resulting crude product was filtered and boiled in ethanol (20 mL). After cooling overnight, the white cotton-like product (0.24g, 23%) was filtered, rinsed with ethanol, and dried. $[M+H]^+$ 413.

Example 2

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one

a) 4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinoline-3-carboxamidine

Trimethyaluminum (11.7 mL, 2.0 M sol. in toluene) was added dropwise to a suspension of 4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinoline-3-carbonitrile (2.0 g, 7.8 mmol) and NH_4Cl (1.25 g, 23.41 mmol) in dioxane (35 mL). The reaction mixture was stirred at room temperature for 1 h, then heated to 85 °C and stirred overnight. The reaction was cooled to room temperature and H_2O (ca. 3 mL) and EtOAc (ca. 250 mL) where then added. After stirring for 15 min, excess solid $NaHCO_3$ was then added, and stirring continued for 1 h. The reaction mixture was then filtered and concentrated. The residue was triturated with Et_2O to afford 1.7 g (80%) of the title compound as a pale yellow solid.

b) 3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one

A suspension of the compound as obtained from Example 2a (150 mg, 0.549 mmol) and (4-chloropyrid-3-yl)sulfonyl chloride (deTullio, P.; Pirotte, B.; Dupont, L.; Masereel, B.; Laeckmann, D.; Podona, T.; Diouf, O.; Lebrun, P.; Delarge, J. *Tetrahedron* 1995, *51* (11), 3221) (140 mg, 0.658 mmol) in THF (7.0 mL) was treated with sodium hydride (87.8 mg, 60% dispersion in mineral oil, 2.20 mmol). The reaction mixture was stirred at room temperature for 1 h, refluxed for 3 h, then cooled to room temperature and poured into a mixture of ice/1M HCl. The resulting precipitate was filtered, washed with H_2O, then with hexane and EtOAc (dropwise) and air dried to give 112 mg of the title compound (46% yield) as a pale yellow powder. ^1H NMR (d_6-DMSO) δ 14.5 (s, 1H), 9.1 (s, 1H), 8.8 (d, 1H, J = 5.7 Hz), 8.2 (dd, 1H, J = 8.1, 1.4 Hz), 7.9 (td, 1H, J = 8.5, 1.4 Hz), 7.7 (m, 2H), 7.5 (t, 1H, J = 7.6 Hz), 4.3 (m, 2H), 1.8 (m, 1H), 1.5 (m, 2H); 1.0 (d, 6H, J = 6.6 Hz). MS(ES+) m/e 413 $[M+H]^+$.

Example 3

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one

A suspension of the compound as obtained from Example 2a (50 mg, 0.183 mmol) and (2-chloropyrid-3-yl)sulfonyl chloride (Byull. Izobr., No. 2 (1978); Inventor's certificate No. 595308.) (75 mg, 0.355 mmol) in THF (4.0 mL) was treated with sodium hydride (75 mg, 60% dispersion in mineral oil, 1.87 mmol). The reaction mixture was stirred at room

temperature for 1 h, refluxed for 3 h, then cooled to room temperature and poured into a mixture of ice/1M HCl. The resulting precipitate was filtered, washed with H_2O, then with hexane and EtOAc (dropwise) and air dried to give 49 mg of the title compound (59% yield) as a pale yellow powder. Further purification was performed by semipreparative HPLC. ^1H NMR ($CDCl_3$) δ 14.9 (s, 1H), 14.8 (bs, 1H), 8.7 (dd, 1H), 8.3 (td, 1H), 7.8(td, 1H), 7.4 (m, 4H), 4.3 (m, 2H), 1.7 (m, 1H), 1.6 (m, 2H); 1.1 (d, 6H). MS(ES+) m/e 413 $[M+H]^+$. Mp: 224.

Example 4

1-(3,3-Dimethyl-butyl)-3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one

a) 2-(-3,3-Dimethyl-butylamino)-nicotinic acid

Following the procedure for Example 1a substituting 3,3-dimethyl-butylamine for 3-methyl-butylamine, the compound was obtained as a light brown solid (6.83 g, 48 %) ^1H NMR (d_6 DMSO) δ 8.2 (d, 1H), 8.1 (bs, 1H), 8.0 (s, 1H), 7.2 (m, 1H), 6.6 (bs, 1H), 3.3 (m, 2H), 1.5 (t, 2H), 1.0 (s, 9H). MS(ES+) m/e 223 $[M+H]^+$.

b) 1-(3,3-Dimethyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione

Following the procedure for Example 1b, the product was obtained as a light brown solid (3.51 g, 63%). ^1H NMR (d_6 DMSO) δ 8.8 (m, 1H), 8.4 (dd, 1H), 7.4 (m, 1H), 4.2 (m, 2H), 1.6 (m, 2H), 1.0 (s, 9H). MS(ES+) m/e 249 $[M+H]^+$.

c) 1-(3,3-Dimethyl-butyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]napthyridine-carbonitrile

A suspension of NaH (2.23 mg, 9.32 mmol) in DMF was treated with methylcyano acetate (924 mg, 9.32 mmol). After five minutes of stirring at room temperature a solution of the compound obtained in Example 4c (925 mg, 3.72 mmol) in 2 ml DMF was added. The solution was heated at 110 °C for 3 hours. An orange solution resulted and was allowed to cool to room temperature before being treated with 10 ml Acetic acid and subjected to reflux for 4 hours. The solution was cooled and poured into cold 3N HCl. The cream color precipitate formed, was filtered, washed with H_2O and ether and then air dried to give 643 mg of the desired compound (64 % yield)

d) 1-(3,3-Dimethyl-butyl)-4-hydroxy-2-oxo-1,2-dyhydro-[1,8]napthyridine-carboxamidine

Following the procedure reported in Example 2a, the compound obtained from Example 4c was converted to the desired product (216 mg, 95%) MS(ES+) m/e 289 $[M+H]^+$.

e) 1-(3,3-Dimethyl-butyl)-3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one

Following the procedure in Example 2b, except substituting 1-(3,3-Dimethyl-butyl)-4-hydroxy-2-oxo-1,2-dyhydro-[1,8]napthyridine-carboxamidine for 4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinoline-3-carboxamidine, the title compound was obtained as a white powder after purification by HPLC (4 mg, 6 %) ^{1}H NMR (d_6-DMSO) δ 14.3 (bs, 1H), 9.1 (s, 1H), 8.9 (dd, 2H,), 8.6 (dd, 1H,), 7.7 (d, 1H,), 7.4 (m, 2H), 4.6 (m, 2H), 1.4 (m, 2H), 1.0 (s, 9H). MS(ES+) m/e 428 $[M+H]^+$.

Example 5

(1,1-Dioxo-1,4-dihydropyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-[1,8]napthyridin-2-one

The title compound was prepared following the sequence described in Example 4a-e but substituting 3-methyl-butylamine for 3,3-dimethyl-butylamine. The product was obtained in 30% yield after purification by HPLC (225 mg, 0.546 mmol) M.P. 196 °C ^{1}H NMR (d_6-DMSO) δ 14.3 (bs, 1H), 9.1 (s, 1H), 8.9 (dd, 2H,), 8.6 (dd, 1H,), 7.7 (d, 1H,), 7.4 (m, 2H), 4.6 (m, 2H), 1.7 (q, 1H), 1.6 (m, 2H), 1.0 (d, 6H). MS(ES+) m/e 414 $[M+H]^+$.

Example 6

1-(3,3-Dimethyl-butyl)-3-(1,1-dioxo-4*H*-1,4-dihydropyrido[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one

Following the procedure from Example 3, but substituting 1-(3,3-dimethyl-butyl)-4-hydroxy-2-oxo-1,2-dyhydro-[1,8]napthyridine-carboxamidine for 4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinoline-3-carboxamidine, the title compound was obtained as a white powder after purification by HPLC (3.6 mg, 5 %) ^{1}H NMR ($CDCl_3$) δ 14.9 (s, 1H), 14.8 (s, 1H), 8.8 (d, 1H,), 8.7 (d, 1H,), 8.5 (d, 1H,), 8.3 (d, 1H), 7.4 (m, 1H), 7.3 (m, 1H), 4.6 (m, 2H), 1.3 (m, 2H), 1.0 (s, 9H). MS(ES+) m/e 428 $[M+H]^+$.

Example 7

6-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-7-hydroxy-4-(3-methyl-butyl)-4H-thieno[3,2-b]pyridin-5-one

a) 1-(3-Methyl-butyl)-1H-thieno[3,2-d][1,3]oxazine-2,4-dione

2-Thioisatoic anhydride (0.34g, 2.0 mmol) was suspended in DMA (5 mL). Sodium hydride (1.1 eq, 2.2 mmol, 0.087g of a 60% dispersion in mineral oil) was added, and the mixture was allowed to stir for 30 minutes. A solution of 1-bromo-3-methylbutane (1.0 eq, 2.0 mmol, 0.30g) in DMA was added, and the mixture was allowed to stir at room temperature under nitrogen overnight. The reaction mixture was poured into ice water and stirred vigorously for 15 minutes. The resulting tan powder (0.17g, 36%) was filtered and dried.

b) 6-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-7-hydroxy-4-(3-methyl-butyl)-4H-thieno[3,2-b]pyridin-5-one

Following the procedure of Example 1c, except substituting 1-(3-methyl-butyl)-1H-thieno[3,2-d][1,3]oxazine-2,4-dione for 1-(3-methyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione, the target compound was obtained as a pale yellow solid (0.17g, 58%). $[M+H]^+$ 418.

Example 8

5-(1,1 Dioxo-4H-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-7-(3-methyl-butyl)-7H-thieno[2,3-b]pyridin-6-one

a) 1*H*-Thieno[2,3-d][1,3]oxazine-2,4-dione

2-Amino-thiophene-3-carboxylic acid methyl ester (*Dyes Pigm.* 1995, 33(4), 319) (500 mg, 3.18 mmol) was suspended in water (6.0 mL) containing potassium hydroxide (357 mg, 6.36 mmol) and the mixture was refluxed for 15 min. The reaction was cooled to 0°C and phosgene (496 mg, 5.01 mmol, 2.5 mL of 20% in toluene solution) was added via syringe. After addition was complete, the reaction was allowed to warm to room temperature over 1 h. The reaction was filtered and the solid obtained was washed with water and petroleum ether and air dried to give the title compound as a tan solid (440 mg, 82%). ^{1}H NMR (d_6-DMSO) δ 7.21-7.15 (m, 2H), 12.6 (br s, 1H).

b) 1-(3-Methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione

A solution of the compound as obtained from Example 8a) (418 mg, 2.47 mmol) and 1-iodo-3-methylbutane (499 mg, 2.52 mmol) in DMF (12 mL) was treated with solid potassium carbonate (416 mg, 3.01 mmol) and stirred at room temperature overnight. The reaction was diluted with water and filtered. The solid obtained was washed with petroleum ether and air dried to give the title compound as a tan solid (233 mg, 40%). ^{1}H-NMR (d_6-DMSO) δ 7.31 (d,1H), 6.91 (d, 1H), 3.93 (t, 2H), 1.7 (m, 3H), 1.01 (d,6H). MS(ES+) m/e 240 $[M+H]^+$.

c) 5-(1,1 Dioxo-4H-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-7-(3-methyl-butyl)-7H-thieno[2,3-b]pyridin-6-one

Following the procedure of Example 1c), except substituting 1-(3-methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione for 1-(3-methyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione , the title compound was obtained as a pale green solid (60.1 mg, 41%). ^{1}H NMR (d_6-DMSO) δ 14.8 (br s, 1H), 14.1 (br s, 1H), 7.91 (m, 1H), 7.74 (m, 1H), 7.67 (m, 1H), 7.55 (m, 1H), 7.49 (m, 1H), 7.42 (m, 1H), 4.14 (t, 2H), 1.72-1.62 (m, 3H), 0.98 (d, 6H). MS(ES+) m/e 418 $[M+H]^+$.

Example 9

2-Bromo-5-(1,1-dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadiazine-3-yl)-4-hydroxy-7-(3-methyl-butyl)-7*H*-thieno[2,3-b]pyridin-6-one

a) 6-Bromo-1-(3-methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione

A solution of the compound as obtained in Example 8b) (107.8 mg, 0.45 mmol) and N-Bromosuccinimide (97.2 mg, 0.546 mmol) in 1:1 $CHCl_3$:HOAc (2 mL) was stirred at room temperature for 4.5 h. The reaction was diluted with water and chloroform, washed with 1.0 M potassium hydroxide solution, water, and brine, dried (Na_2SO_4), and concentrated on a rotary evaporator to yield the title compound as a brown solid (106.5 mg, 75%). ^{1}NMR (d_6-DMSO) δ 7.5 (s, 1H), 3.8 (t,2H), 1.6 (m 3H), 0.93 (d, 6H). MS(ES+) m/e 318 $[M+H]^+$.

b) 2-Bromo-5-(1,1-dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadiazine-3-yl)-4-hydroxy-7-(3-methyl-butyl)-7*H*-thieno[2,3-b]pyridin-6-one

Following the procedure of Example 8c), except substituting 6-bromo-1-(3-methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione for 1-(3-methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione, the title compound was prepared as a pale green solid (73.9 mg, 61%). ^{1}H NMR (d_6-DMSO) δ 14.8 (br s, 1H), 13.9 (br s, 1H), 7.91 (d, 1H), 7.76 (m, 1H), 7.65 (m, 2H), 7.54 (m, 1H), 4.07 (t, 2H), 1.75-1.60 (m, 3H), 0.97 (d, 6H). MS(ES+) m/e 496 $[M+H]^+$.

Example 10

3-(7-Bromo-6-Chloro-1,1-dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one

A solution of the compound as obtained from Example 2a) (150 mg, 0.549 mmol) and 4-bromo-2,5-dichloro-thiophene-3-sulfonyl chloride (199 mg, 0.604 mmol) in DMF (5.0 mL) was treated with sodium hydride (87.8 mg, 60% dispersion in mineral oil, 2.20 mmol). The reaction mixture was stirred at room temperature for 1 h, then at 95 °C overnight. The reaction was cooled to room temperature and poured into a mixture of ice/1M HCl. The resulting precipitate was filtered and air dried to give 179 mg of the title compound. A portion (75 mg) was recrystallized from warm dimethyl sulfoxide to give 67 mg of the title compound as pink solid. ^{1}H NMR ($CDCl_3$) δ 15.6 (s, 1H), 14.7 (s, 1H), 8.3 (dd, 1H, J = 8.2, 1.2 Hz), 7.8 (td, 1H, J = 8.2, 1.6 Hz), 7.5-7.4 (m, 2H), 4.3 (m, 2H), 1.83 (quin, 1H, J = 6.6 Hz), 1.7-1.6 (m, 2H); 1.1 (d, 6H, J = 6.6 Hz). MS(ES+) m/e 530 $[M+H]^+$.

Example 11

3-(6-Chloro-1,1-dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one

A suspension of the compound obtained in Example 9b) (80 mg, 0.151 mmol) and Zn powder (49.3 mg, 0.753 mmol) in AcOH (3 mL) and H_2O (0.200 mL) was stirred at 50 °C for 1.5 h, then at 100 °C for 3 h. After addition of another portion of Zn powder (ca 30 mg) and AcOH (1 mL) the reaction was refluxed for 48 h. The mixture was cooled to room temperature and poured into $H_2O/CHCl_3$. The separated organic layer was washed with $NaHCO_3$ (5% aq. sol.), dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (0.5% MeOH in $CHCl_3$) to afford 22 mg (yield, 32%) of the title

compound and 8 mg of the bis-dehalogenated material. ^{1}H-NMR ($CDCl_3$) δ 15.4 (s, 1H), 14.8 (s, 1H), 8.3 (dd, 1H, *J* = 8.1, 1.4 Hz), 7.8-7.7 (m, 1H), 7.4-7.3 (m, 2H), 7.1 (s, 1H), 4.4-4.3 (m, 2H), 1.9-1.6 (m, 3H), 1.1 (d, 6H, *J* = 6.6 Hz). MS(ES+) m/e 452 $[M+H]^+$.

Example 12

3-(5,7-Dimethyl-1,1-dioxo-4*H*-1,4-dihydro-5*H*-pyrazo[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one

A solution of the compound as obtained from Example 2a) (300 mg, 1.1 mmol) and 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-sulfonyl chloride (277 mg, 1.2 mmol) in DMF (10.0 mL) was treated with sodium hydride (176 mg, 60% dispersion in mineral oil, 4.39 mmol). The reaction mixture was stirred at room temperature for 1 h, then at 80 °C for 20 min and 40 °C overnight. An additional portion of NaH (ca. 75 mg) was then added and the reaction mixture was stirred at 80 °C for 1 h. The reaction was cooled to room temperature and poured into a mixture of ice/1M HCl. The resulting precipitate was filtered, washed with H_2O, then with Et_2O and hexane and air dried to give 364 mg of the title compound (77% yield) as a white powder. ^{1}H NMR ($CDCl_3$) δ 15.8 (s, 1H), 15.1 (s, 1H), 8.3 (dd, 1H, *J* = 8.1, 1.5 Hz), 7.7 (m, 1H), 7.3 (m, 2H), 4.3 (m, 2H), 3.9 (s, 3H), 2.5 (s, 3H), 1.8 (m, 1H), 1.6 (m, 2H); 1.1 (d, 6H, *J* = 6.5 Hz). MS(ES+) m/e 430 $[M+H]^+$.

Example 13

3-(1,1-Dioxo-1,4-dihydro-thieno[2,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one

The compound from Example 10 (0.200 g, 0.378 mmol) in ethanol (10.0 mL) and methanol (5.0 mL) with NaOH and a catalytic amount of 10% palladium on carbon was hydrogenated (50 psi) overnight. The reaction was filtered through celite, washed (ethyl acetate, methanol), the collected solvent was dried ($MgSO_4$), filtered, and evaporated under vacuum to give the title compound (0.150 g, 95%). ^{1}H NMR (400MHz, d_6-DMSO) δ 8.03 (1H, d, *J* = 7.8 Hz); 7.37 (1H, t, *J* = 6.8 Hz); 7.17 (1H, d, *J* = 8.3 Hz); 7.03 (1H, d, *J* = 5.8 Hz); 6.97 (1H, t, *J* = 7.5 Hz); 4.08 (2H, m); 1.71 (1H, m); 1.45 (2H, m); 0.98 (6H, d, *J* = 6.6 Hz). MS(ES+) m/e 418 $[M+H]^+$.

Example 14

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(tetrahydro-furan-3-ylmethyl)-1H-quinolin-2-one

a) 1-(Tetrahydro-furan-3-ylmethyl)-1 *H* – benzo[1,3]oxazine-2,4-dione

Tetrahydro-3-furanmethanol (1.30 mL, 13.5 mmol) and triphenylphosphine (5.00 g, 19.1 mmol) were added to a suspension of isatoic anhydride (2.00 g, 12.3 mmol) in CH_2Cl_2 (10.0 mL). Diisopropyl azodicarboxylate (2.66 mL, 13.5 mmol) was added dropwise. The solution was stirred at room temperature for 20h, then the solvent was evaporated at reduced pressure. Flash Chromatography (25% ethyl acetate in hexanes) gave the title compound.

b) 4-Hydroxy-2-oxo-1-(tetrahydro-furan-3-yl-methyl)-1,2-dihydro-quinoline-3-carbonitrile

Sodium Hydride (60% dispersion in mineral oil, 0.777 g, 19.4 mmol) was washed with hexane and suspended in dimethylformamide. Methyl cyanoacetate (0.856 mL, 9.72 mmol) and the compound from Example 14a) (1.20 g, 4.86 mmol) were added and the mixture was stirred at 110°C for 3h. The solution was poured onto 1N HCl, and the solid formed was collected by vacuum filtration to give the title compound.

c) 4-Hydroxy-2-oxo-1-(tetrahydro-furan-3-ylmethyl)-1,2-dihydro-quinoline-3-carboxamidine

The procedure from Example 2a) was followed here using 4-hydroxy-2-oxo-1-(tetrahydro-furan-3-yl-methyl)-1,2-dihydro-quinoline-3-carbonitrile (0.269 g, 0.990 mmol) in the place of 4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinoline-3-carbonitrile, trimethylaluminum in toluene (2.0 M, 1.48 mL, 2.96 mmol) and NH_4Cl (0.159 g, 2.96 mmol) in dioxane (5.0 mL) to give the title compound.

d) 3-(1,1-Dioxo-1,4-dihydro-1-pyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(tetrahydro-furan-3-ylmethyl)-1 *H* –quinolin-2one

The procedure from Example 2b) was followed here using 4-hydroxy-2-oxo-1-(tetrahydro-furan-3-ylmethyl)-1,2-dihydro-quinoline-3-carboxamidine (0.103 g, 0.360 mmol) in the place of 4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinoline-3-carboxamidine, 4-chloro-pyridine-3-sulfonyl chloride (0.091 g, 0.430 mmol), and NaH (60% dispersion in mineral oil, 0.057 g, 1.44 mmol) in tetrahydrofuran (8.0 mL) to yield the title compound (0.076 g, 50%). MS(ES+) m/e 427 $[M+H]^+$.

Example 15

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-pentyl)-1H-quinolin-2-one

a) 1-(3-Methyl-pentyl)-1H-benzo[d][1,3]oxazine-2,4-dione

The procedure from Example 14a) was followed here, using 3-methyl-1-pentanol (0.840 mL, 6.75 mmol) in the place of tetrahydro-3-furanmethanol, isatoic anhydride (1.00 g, 6.13 mmol), triphenylphosphine (2.25 g, 9.60 mmol), and diisopropyl azodicarboxylate (1.33 mL, 6.75 mmol) in CH_2Cl_2 (20.0 mL) to give the title compound.

b) 4-Hydroxy-1-(3-methyl-pentyl)-2-oxo-1,2-dihydro-quinoline-3-carbonitrile

The procedure from Example 14b) was used here using the compound from Example 15a) (0.770 g, 3.12 mmol) in the place of the compound from Example 14a) and NaH (0.50 g, 12.5 mmol) and methyl cyanoacetate (0.550 mL, 6.24 mmol) in dimethylformamide (10.0 mL) to give the title compound.

c) 4-Hydroxy-1-(3-methyl-pentyl)-2-oxo-1,2-dihydro-quinoline-3-carboxamidine

The procedure from Example 2a) was followed here using the compound from Example 15b) (0.647 g, 2.38 mmol) in the place of 4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinoline-3-carbonitrile, $(CH_3)_3Al$ in toluene (2.0 M, 3.57 mL, 7.14 mmol) and NH_4Cl (0.381 g, 7.14 mmol) in dioxane (10.0 mL) to give the title compound.

d) 3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-pentyl)-1H-quinolin-2-one

The procedure from Example 14d) was used here using the compound from Example 15c) (0.100 g, 0.340 mmol) in the place of the compound from Example 14c) to yield the title compound. MS(ES+) m/e 427 $[M+H]^+$.

Example 16

3-(1,1-Dioxo-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one

A suspension of the compound from Example 2b) (0.150 g, 0.360 mmol) in acetic acid (15.0 mL) was stirred under H_2 at room temperature overnight in the presence of catalytic amount of platinum oxide. The mixture was filtered through celite, the solvent

evaporated under vacuum and the residue freeze dried to give the title compound (0.126 g, 83%). ^{1}H NMR (400MHz, d_6-DMSO) δ 13.8 (1H, s); 11.9 (1H, s); 8.1 (1H, d); 7.9 (1H, t); 7.6 (1H, d); 7.4 (1H, t); 4.3 (2H, m); 4.1 (2H, s); 3.4 (2H, t); 2.9 (2H, t); 1.8 (1H, m); 1.5 (2H, t); 1.0 (6H, d).

Example 17

3-(7-Acetyl-1,1-dioxo-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one

The compound from Example 16 (0.020 g, 0.048 mmol) was combined with acetic anhydride (0.005 g, 0.048 mmol), pyridine (0.015 g, 0.192 mmol) and a catalytic amount of dimethylaminopyridine in CH_2Cl_2 (5 mL). After stirring overnight, the solvent was evaporated under vacuum and the residue was dissolved in dimethylsulfoxide. Purification by reverse phase HPLC gave the title compound (0.0075 g, 34%). MS(ES+) m/e 459 $[M+H]^+$.

Example 18

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1*H*-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-acetic acid methyl ester

The compound from Example 16 (0.020 g, 0.048 mmol) was added to NaH (60% dispersion in mineral oil, 0.004 g, 0.100 mmol) in tetrahydrofuran (2.0 mL). After stirring for 15 minutes, bromomethyl acetate (0.0153 g, 0.100 mmol) was added and the reaction mixture was stirred at room temperature overnight. Flash Chromatography (3% NH_4OH, 30% CH_3OH in CH_2Cl_2) gave the title compound (0.0025 g, 11%). MS(ES+) m/e 489 $[M+H]^+$.

Example 19

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-propionitrile

The compound from Example 16 (0.280 g, 0.670 mmol) was dissolved in methanol (5.0 mL) and tetrahydrofuran (10.0 mL) and added to acrylonitrile (0.180 mL, 2.69 mmol) and diisopropylethylamine (0.290 mL, 1.28 mmol). The solution was stirred for three days at room temperature. Flash Chromatography (50% ethyl acetate in hexane) gave the title compound (0.120 g, 38%). MS(ES+) m/e 470 $[M+H]^+$.

Example 20

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-acetic acid

The compound from Example 18 (0.010 g, 0.021 mmol) was added to 2N NaOH and tetrahydrofuran and stirred overnight. The reaction was acidified with acetic acid and poured onto H_2O. The solid obtained was filtered, and washed (ethyl ether, hexane) to give the title compound (0.003 g, 24%). MS(ES+) m/e 475 $[M+H]^+$.

Example 21

3-[7-(3-Amino-propyl)-1,1-dioxo-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl]-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one

The compound from Example 19 (0.020 g, 0.043 mmol) was hydrogenated overnight in acetic acid and a catalytic amount of platinum oxide. The suspension was filtered through celite and the solvent was poured into H_2O. The solid obtained was collected by filtration and washed (water, ethyl ether, hexane) to give the title compound (0.014 g, 69%). MS(ES+) m/e 474 $[M+H]^+$.

Example 22

3-(1,1-Dioxo-1,4-dihydro-1-thia-2,4,8-triaza-naphthalen-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one trifluoroacetate

a) (1,1-Dioxo-1,4-dihydro-1-thia-2,4,8-triaza-naphthalen-3-yl)-acetic acid ethyl ester

To 3-amino-pyridine-2-sulfonic acid amide (0.30 g, 1.73 mmol) was added 3,3,3-triethoxy-propionic acid ethyl ester (0.811 g, 3.47 mmol) and *p*-toluene sulfonic acid (0.329 g, 1.75 mmol) in dimethylformamide (50.0 mL) and stirred at room temperature overnight.

The material was dried under vacuum and dissolved in dimethylsulfoxide (6.0 mL). Purification by reverse phase HPLC gave the title compound (0.063 g, 13.5%).

b) 3-(1,1-Dioxo-1,4-dihydro-1-thia-2,4,8-triaza-naphthalen-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one trifluoroacetate

The compound from Example 22a) (0.063 g, 0.234 mmol) was added to NaH (60% dispersion in mineral oil, 0.023 g, 0.535 mmol) in anhydrous dimethylformamide (1.5 mL). Then, 1-(3-methyl-butyl)-1H-benzo[1,3]oxazine-2,4-dione (0.055 g, 0.234 mmol) was added, and the reaction was refluxed for 3h. After cooling to room temperature, acetic acid (3.0 mL) was added, and the mixture was refluxed for another 1h. The mixture was cooled and poured into cold 3N HCl. The precipitate was collected and washed (ethyl ether) to give the title compound (0.025 g, 26%). MS(ES+) m/e 413 $[M+H]^+$.

Example 23

3-{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-propionamide

The compound from Example 19 (0.008 g, 0.017 mmol) was dissolved in H_2SO_4 (2.0 mL). After adding 5% H_2O (0.1 mL), the reaction was stirred for three days to give the title compound (0.006 g, 69%). ^{1}H NMR (400MHz, d_6-DMSO) δ 13.7 (1H, s); 8.1 (1H, d); 7.85 (1H, t); 7.6 (1H, d); 7.35 (1H, t); 4.2 (2H, m); 3.4 (2H, m); 2.9 (2H, s); 2.75 (2H, m); 1.65 (1H, m); 1.4 (2H, m); 0.9 (6H, d).

Example 24

5-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-methyl-7-(3-methyl-butyl)-1,7-dihydro-pyrazolo[3,4-b]pyridin-6-one

a) Ethyl 1-methyl-5-(3-methyl-butylamino)-1*H*-pyrazole-4-carboxylate

A solution of ethyl 1-methyl-1*H*-pyrazole-4-carboxylate (1.00 g, 5.91 mmol) in anhydrous methylene chloride (50.0 mL) was treated with isovaleraldehyde (0.761 mL, 7.09 mmol) and sodium triacetoxyborohydride (1.50 g, 7.09 mmol). After stirring 3 d at ambient temperature, the reaction mixture was quenched with 1M aqueous hydrochloric acid, diluted with brine, extracted thrice with methylene chloride, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified *via* flash column chromatography (20% ethyl acetate in hexanes) to give the title compound as a clear, colorless oil (0.620 g, 44%). ^{1}H NMR

(300MHz, $CDCl_3$) δ 7.62 (s, 1H), 5.67 (br s, 1H), 4.25 (q, J = 7 Hz, 2H), 3.77 (s, 3H), 3.26 (t, J = 7 Hz, 2H), 1.78-1.62 (m, 1H), 1.49 (q, J = 7 Hz, 2H), 1.33 (t, J = 7 Hz, 3H), 0.92 (d, J = 7 Hz, 6H). MS(ES+) m/e 240 $[M+H]^+$.

b) 5-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-methyl-7-(3-methyl-butyl)-1,7-dihydro-pyrazolo[3,4-b]pyridin-6-one

A solution of the compound from Example 24a) (0.320 g, 1.34 mmol) and ethyl 1,1-dioxo-1,4-dihydro-1-benzo[1,2,4]thiadiazin-3-yl-acetate (prepared by the method of Kovalenko, S. N.; Chernykh, V. P.; Shkarlat, A. E.; Ukrainets, I. V.; Gridasov, V. I.; Rudnev, S. A. *Chem. Heterocycl. Compd. (Engl. Trans.)* 1998, *34*, 791) (0.359 g, 1.34 mmol) in anhydrous *N,N*-dimethylformamide (10.0 mL) was treated with sodium hydride (60% dispersion in mineral oil) (0.128 g; 5.35 mmol) and heated to 105 °C. After stirring 3 d at 105 °C, the reaction mixture was allowed to cool to ambient temperature and treated with glacial acetic acid (3.0 mL). The reaction was heated to reflux for 3 h then cooled to ambient temperature and poured into 1M aqueous hydrochloric acid. The solution was diluted with brine, extracted thrice with ethyl acetate, dried over magnesium sulfate, filtered, concentrated in vacuo, and triturated with methanol to give the title compound as a light yellow solid (0.040 g, 7%). ^{1}H NMR (300MHz, $CDCl_3$) δ 15.0 (s, 1H), 14.1 (s, 1H), 7.97 (d, J = 7 Hz, 1H), 7.96 (s, 1H), 7.61 (t, J = 7 Hz, 1H), 7.42 (t, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 1H), 4.34 (t, J = 8 Hz, 2H), 4.22 (s, 3H), 1.84-1.72 (m, 1H), 1.67-1.54 (m, 2H), 0.88 (d, J = 8 Hz, 6H). MS(ES+) m/e 416 $[M+H]^+$.

Example 25

5-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-7-(3-methyl-butyl)-1,7-dihydro-pyrazolo[3,4-b]pyridin-6-one

A solution of the compound from Example 24b) (0.015 g, 0.160 mmol) in glacial acetic acid (2.5 mL) was treated with aqueous hydrogen bromide (48%, 0.5 mL) and heated to reflux for 2 d. The reaction mixture was allowed to cool to ambient temperature and treated with H_2O (3.0 mL). The resulting precipitate was filtered and dried in vacuo to give the title compound as a white solid (0.013 g, 90%). ^{1}H NMR (300MHz, $CDCl_3$) δ 15.1 (s, 1H), 14.5 (s, 1H), 8.16 (s, 1H), 7.99 (d, J = 8 Hz, 1H), 7.64 (t, J = 8 Hz, 1H), 7.45 (t, J = 8

Hz, 1H), 7.32 (d, J = 8 Hz, 1H), 5.31 (s, 1H), 4.19 (t, J = 8 Hz, 2H), 1.82-1.72 (m, 1H), 1.68-1.55 (m, 2H), 0.87 (d, J = 8 Hz, 6H). MS(ES+) m/e 402 $[M+H]^+$.

Example 26

3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazine-7-carboxylic acid phenylamide

The compound from Example 16 (0.050 g, 0.120 mmol) in CH_2Cl_2 (6.0 mL) was added to phenyl isocyanate (0.013 mL, 0.120 mmol) and stirred overnight under nitrogen. The solvent was removed under vacuum. Flash Chromatography (0-10% methanol in chloroform) of the residue gave the title compound (0.022 g, 34%). ^{1}H NMR (400MHz, d_6-DMSO) δ 8.2 (1H, m); 7.9 (1H, m); 7.7 (1H, m); 7.5 (3H, m); 7.3 (2H, m); 7.0 (1H, m); 4.5 (1H, s); 4.35 (2H, m); 3.8 (2H, m); 1.8 (1H, m); 1.6 (2H, m); 1.1 (6H, d).

Example 27

3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazine-7-carboxylic acid methylamide

The procedure from Example 26 was followed here using methyl isocyanate (0.007 g, 0.120 mmol) in the place of phenyl isocyanate. Flash Chromatography (0-10% methanol in chloroform) gave the title compound (0.010 g, 17%). ^{1}H NMR (400MHz, d_6-DMSO) δ 14.8 (1H, s); 13.5 (1H, s); 8.1 (1H, m); 7.9 (1H, m); 7.6 (1H, m); 7.4 (1H, m); 4.4 (3H, s); 1.8 (1H, m); 1.5 (2H, m); 1.0 (6H, d).

Example 28

3-[7-Ethyl-1,1-dioxo-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one

The compound from Example 16 (0.014 g, 0.034 mmol) was combined with iodoethane (0.054 mL, 0.067 mmol) and NaH (60% dispersion in mineral oil, 0.003 g, 0.067 mmol) in dimethylformamide. After stirring overnight, the reaction was poured onto H_2O to form a precipitate which was collected and purified by flash chromatography (0-10% CH_3OH in $CHCl_3$) to give the title compound (7.5 mg, 50%). MS(ES+) m/e 445 $[M+H]^+$.

Example 29

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4,6-dihydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one

a) (1,1-dioxo-1,4-dihydro-1-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-acetic acid ethyl ester

To 4-amino-pyridine-3-sulfonic acid amide (0.050 g, 0.29 mmol) was added 3,3,3-triethoxy-propionic acid ethyl ester (0.270 g, 1.15 mmol) and *p*-toluene sulfonic acid (0.100 g, 0.580 mmol). After stirring at room temperature for 3 days, the precipitate was removed and the filtrate was dried under vacuum. The residue was added to ethyl acetate and washed (H_2O). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash Chromatography (0-10% CH_3OH in $CHCl_3$) gave the title compound.

b) 3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4,6-dihydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one

The compound from Example 29a) (0.02 g, 0.074 mmol) was dissolved in anhydrous dimethylformamide (3.0 mL). NaH (60% dispersion in mineral oil, 0.012 g, 0.296 mmol) was added and the reaction was stirred for 5 min at room temperature. Then 6-(*tert*-butyl-dimethyl-silyloxy)-1-(3-methyl-butyl)-1-benzo[1,3]oxazine-2,4-dione (0.027 g, 0.075 mmol) in dimethylformamide (2.0 mL) was added and the reaction was stirred at 80°C for 3h. After cooling, acetic acid was added for a colorless, transparent solution. The reaction was stirred at 85°C for 1h, cooled, and the precipitate was collected to give the title compound. MS(ES+) m/e 429 $[M+H]^+$.

Example 30

3-[1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-6-yloxy]-acetonitrile

The compound from Example 29b) (0.100 g, 0.230 mmol) was added to K_2CO_3 (0.103 g, 0.750 mmol) and KI (0.0415 g, 0.250 mmol) in DMF (5 mL) and heated to 80°C. Bromoacetonitrile (0.031 mL, 0.250 mmol) was added and the reaction was heated and stirred overnight. The mixture was filtered, the residue was washed with acetone and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (0-5% CH_3OH in $CHCl_3$) to give the title compound (0.061 g, 57%). MS(ES+) m/e 468 $[M+H]^+$.

Example 31

3-{1,1-Dioxo-7-[2-(2H-tetrazol-5-yl)-ethyl]-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl}-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one

The compound from Example 19 (0.015 g, 0.032 mmol) was added to azidotrimethylsilane (0.015 g, 0.128 mmol) and dibutyltin oxide (0.790 mg, 0.003 mmol) in toluene (2 mL). The mixture was microwaved for 105 min at 100°C, cooled, filtered, and the solid was washed (ethyl ether, hexane) and dried to give the title compound (0.011 g, 60%). ^{1}H NMR (400MHz, d_6-DMSO) δ 8.05 (1H, d); 7.4-7.55 (2H, m); 7.2 (1H, d); 7.0-7.1 (1H, m); 4.05 (2H, m); 3.1 (3H, m); 2.85 (2H, m); 2.75 (2H, m); 1.7 (1H, m); 1.4 (2H, m); 0.95 (6H, d).

Example 32

3-(1,1-Dioxo-7-oxy-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one

The compound from Example 2b), 3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one, (200 mg, 0.485 mmol), was dissolved in acetic acid (5.0 mL) and 30 % hydrogen peroxide (0.65 mL) was added. The mixture was stirred at 65°C for 14 hours. The reaction mixture was cooled to room temperature and activated charcoal (100 mg) was added. The mixture was filtered through celite and the solvents removed under vacuum to give the product as a yellow powder (120 mg, 58%). ^{1}NMR (d_6-DMSO) δ 14.6 (br s, 1H), 8.8 (s, 1H), 8.5 (dd, 1H, J = 7.3, 2.0 Hz), 8.2 (dd, 1H, J = 8.1, 1.5 Hz), 7.9 (m, 2H), 7.7 (d, 2H, J = 8.7 Hz), 7.5 (t, 1H, J = 7.7 Hz), 4.3 (t, 2H, J = 8.2 Hz), 1.8 (m, 1H), 1.5 (m, 2H); 1.0 (d, 6H, J = 6.6 Hz). MS(ES+) m/e 429 $[M+H]^+$.

Example 33

3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-Dioxo-1,7 -dihydropyrido[4,3-*e*][1,2,4]thiadiazin-8-one

A solution of the product obtained in Example 33, 3-(1,1-Dioxo-7-oxy-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one, (15 mg, 0.035 mmol) in acetic anhydride (1 mL) was refluxed for six hours. The solvent was removed by vacuum and the crude material dissolved in methanol (0.5 mL) and water (0.5 mL) and stirred at room temperature for 1 hour. The solvent was removed *en*

vacuo. Purification by reverse phase HPLC gave the title compound (8 mg, 53 %) as a white powder. ^{1}H NMR (d_6-DMSO) δ 14.2 (brs, 1H), 12.1 (brs, 1H) 8.2 (dd, 1H), 7.9 (t, 1H), 7.7 (t, 1H), 7.4 (t, 1H), 6.4 (d, 1H,), 4.3 (m, 2H), 1.8 (m, 1H), 1.5 (m, 2H); 1.0 (d, 6H, *J* = 6.6 Hz). MS(ES+) m/e 429 $[M+H]^+$.

Example 34

1-(2-Cyclopropyl-ethyl)-3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-6-fluoro-4-hydroxy-1*H*-quinolin-2-one

a) 1-(2-Cyclopropyl-ethyl)-6-fluoro-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonitrile

Following the procedure of Example 4c), except substituting 1-(2-cyclopropyl-ethyl)-6-fluoro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione for 1-(3,3-dimethyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione, the title compound was obtained in 88% yield.

b) 1-(2-Cyclopropyl-ethyl)-6-fluoro-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxamidine

Following the procedure reported in Example 2a), the compound obtained from Example 4c) was converted to the desired product (216 mg, 95%). MS(ES+) m/e 292 $[M+H]^+$.

c) 1-(2-Cyclopropyl-ethyl)-3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-6-fluoro-4-hydroxy-1*H*-quinolin-2-one

Following the procedure in Example 2b), except substituting 1-(2-cyclopropyl-ethyl)-6-fluoro-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxamidine for 4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinoline-3-carboxamidine, the title compound was obtained as a yellow powder after purification by HPLC (35 mg, 25 %) ^{1}H NMR ($CDCl_3$) δ 14.9 (s, 1H), 14.8 (s, 1H) 9.1 (s, 1H), 8.7 (s, 1H,), 7.9 (dd, 1H,), 7.5 (m, 1H,), 7.4 (m, 1H), 7.15 (d, 1H), 4.3 (m, 2H) 1.6 (m, 2H), 0.7 (m, 1H) 0.5 (m, 2H) 0.1 (d, 2H), MS(ES+) m/e 429 $[M+H]^+$.

Example 35

1-(2-Cyclopropyl-ethyl)-3-(1,1-Dioxo-1,4-dihydro-pyrido[2,3-e][1,2,4]thiadiazin-3-yl)-6-fluoro-4-hydroxy-1*H*-quinolin-2-one

A suspension of the compound as obtained from Example 34b) (200 mg, 0.690 mmol) and (2-chloropyrid-3-yl)sulfonyl chloride (Byull. Izobr., No. 2 (1978); Inventor's

certificate No. 595308.) (219 mg, 1.04 mmol) in THF (5.0 mL) was treated with sodium hydride (138 mg, 60% dispersion in mineral oil, 3.46 mmol). The reaction mixture was stirred at room temperature for 1 h, refluxed for 3 h, then cooled to room temperature and poured into a mixture of ice/1M HCl. The resulting precipitate was filtered, washed with H_2O, then with hexane and EtOAc (dropwise) and air dried to give 95 mg of the title compound (32% yield) as a pale yellow powder. Further purification was performed by semipreparative HPLC. ^{1}H NMR (d_6-DMSO) δ 14.6 (s, 1H), 8.75 (dd, 1H), 8.6 (td, 1H), 8.4(dd, 1H), 7.7 (m, 2H), 7.5 (m, 1H), 4.3 (m, 2H), 1.5 (m, 2H), 0.7 (m, 1H), 0.3 (m, 2H), 0.0 (m, 2H). MS(ES+) m/e 429 $[M+H]^+$.

Example 36

7-Hydroxy-6-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-(3-methyl-butyl)-4H-thieno[3,2-b]pyridin-5-one

a) 1*H*-Thieno[3,2-*d*][1,3]oxazine-2,4-dione

Following the procedure from Example 8a) except substituting 3-amino-thiophene-2-carboxylic acid methyl ester for 2-amino-thiophene-3-carboxylic acid methyl ester the title compound was obtained as a tan solid (850 mg, 79%). ^{1}H NMR (d_6-DMSO) δ 12.23 (bs, 1H); 8.25 (d, J = 5.0 Hz, 1H) ; 6.94 (d, J = 5.3 Hz, 1H).

b) 1-(3-Methyl-butyl)-1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione

A solution of the compound as obtained from Example 36a) (345 mg, 2.04 mmol) was added to a suspension of NaH (60% suspension in mineral oil, 89.76 mg, 2.24 mmol) in DMF (7 mL). After 10 min, 1-iodo-3-methylbutane (0.282 mL, 2.14 mmol) was added, and the reaction mixture was stirred for 20 h at rt, poured onto ice, let it stand for 1 h. The precipitate was collected by filtration, washed with H_2O and hexane and dried to give the title compound (237 mg, 49%) as a tan solid. ^{1}H NMR (d_6-DMSO) δ 8.34 (d, J = 5.3 Hz, 1H); 7.33 (d, J = 5.3 Hz, 1H); 3.96-3.92 (m, 2H); 1.71-1.61 (m, 1H); 1.54-1.49 (m, 2H); 0.93 (d, J = 6.6 Hz, 6H).

c) 7-Hydroxy-6-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-(3-methyl-butyl)-4*H*-thieno[3,2-*b*]pyridin-5-one

Following the procedure of Example 1c), except substituting 1-(3-methyl-butyl)-1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione for 1-(3-methyl-butyl)-1*H*-pyrido[2,3-d][1,3]-

oxazine-2,4-dione and (7-methoxy-1,1-dioxo-1,4-dihydro-benzo-[1,2,4]-thiadiazin-3-yl)-acetic acid ethyl ester for (1,1-dioxo-1,4-dihydro-benzo-[1,2,4]-thiadiazin-3-yl)-acetic acid ethyl ester the title compound was obtained as a tan solid (335 mg, 76%) after collecting the solid by filtration, washing with H_2O, then Et_2O and hexane and drying in vacuum oven. ^1H NMR (d_6-DMSO) δ 14.92 (br s, 1H); 14.32 (br s, 1H); 8.39 (d, J = 5.3 Hz, 1H); 7.68 (m, 1H); 7.51 (d, J = 5.3 Hz, 1H); 7.37-7.34 (m, 2H); 4.29-4.25 (m, 2H); 3.88 (s, 3H); 1.79-1.69 (m, 1H); 1.58-1.52 (m, 2H); 0.97 (d, J = 6.6 Hz, 6H). MS(ES+) m/e 448 $[M+H]^+$.

d) 7-Hydroxy-6-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-(3-methyl-butyl)-4*H*-thieno[3,2-*b*]pyridin-5-one

The compound from Example 36c) (325 mg, 0.726 mmol) was suspended in 10 mL of AcOH. The mixture was warmed until a solution was obtained and then treated with 3 mL of 48% aq. HBr. After refluxing for 2 h, 1.5 mL of 48% aq HBr was added and the mixture was stirred overnight at refluxing temperature, cooled to rt and treated with 5 mL of H_2O. The precipitate was collected, washed with H_2O, then Et_2O and dried to give the title compound (216 mg, 69%) as a tan powder. ^1H NMR (d_6-DMSO) δ 14.99 (br s, 1H); 14.27 (br s, 1H); 10.42 (s, 1H); 8.38 (d, J = 5.5 Hz, 1H); 7.58-7.55 (m, 1H); 7.51 (d, J = 5.3 Hz, 1H); 7.17-7.15 (m, 2H); 4.28-4.24 (m, 2H); 1.78-1.68 (m, 1H); 1.58-1.52 (m, 2H); 0.97 (d, J = 6.5 Hz, 6H). MS(ES+) m/e 434 $[M+H]^+$.

Example 37

4-Hydroxy-3-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1-(3-methyl-butyl)-1H-[1,8]naphthyridin-2-one

Following the procedure of Example 1c), except substituting (7-methoxy-1,1-dioxo-1,4-dihydro-benzo-[1,2,4]-thiadiazin-3-yl)-acetic acid ethyl ester for (1,1-dioxo-1,4-dihydro-benzo-[1,2,4]-thiadiazin-3-yl)-acetic acid ethyl ester the title compound was obtained as a tan powder (390 mg, 59%) after collecting the solid by filtration, washing with H_2O, then Et_2O and hexane and drying in vacuum oven. ^1H NMR (d_6-DMSO) δ 15.20 (br s,1H); 14.01 (br s, 1H); 8.89 (dd, J = 4.6, 1.8 Hz, 1H); 8.55 (dd, J = 7.9, 1.8 Hz, 1H); 7.74-7.71 (m, 1H); 7.50 (dd, J = 8.0, 4.6 Hz, 1H); 7.38-7.36 (m, 2H); 4.50-4.46 (m, 2H); 3.88 (s, 3H); 1.74-1.64 (m, 1H); 1.60-1.64 (m, 2H); 0.98 (d, J = 6.6 Hz, 6H). MS(ES+) m/e 443 $[M+H]^+$.

Example 38

4-Hydroxy-3-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1-(3-methyl-butyl)-1H-[1,8]naphthyridin-2-one

The compound from Example 37 (350 mg, 0.791 mmol) was suspended in AcOH (14 mL) and warned until a homogeneous solution was obtained. The mixture was then treated with 4 mL of 48% aq HBr and refluxed for 2 h. Additional 48% aq HBr was added and stirring was continued overnight at reflux temperature. Refluxing was continued for 4 h after the addition of 2 mL 48% aq HBr, for 2 h after the addition of 1 mL 48% aq HBr, and for 1.5 h after the addition of 1 mL 48% aq HBr. The reaction mixture was then cooled to rt and diluted with 5 mL of H_2O. The precipitate was collected and washed with H_2O, then Et_2O and dried to give the title compound (300 mg, 74%) as a yellow-green powder as the hydrobromide salt. ^{1}H NMR (d_6-DMSO) δ 15.27 (br s,1H); 13.93 (br s, 1H); 8.89 (dd, J = 4.7, 1.9 Hz, 1H); 8.55 (dd, J = 7.8, 1.7 Hz, 1H); 7.61-7.58 (m, 1H); 7.48 (dd, J = 8.0, 4.5 Hz, 1H); 7.18-7.15 (m, 2H); 4.47-4.44 (m, 2H); 1.72-1.62 (m, 1H); 1.57-1.52 (m, 2H); 0.96 (d, J = 6.3 Hz, 6H). MS(ES+) m/e 429 $[M+H]^+$.

Example 39

4-Hydroxy-5-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one

a) 4-Hydroxy-5-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one

Following the procedure of Example 36c), except substituting 1-(3-methyl-butyl)-1*H*-pyrido[2,3-d][1,3]-oxazine-2,4-dione for 1-(3-methyl-butyl)-1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione the title compound was obtained as a brown powder (125 mg, 61%). ^{1}H NMR (d_6-DMSO) δ 14.87 (br s, 1H); 14.08 (br s, 1H); 7.69-7.67 (m, 1H); 7.48 (d, J = 5.5 Hz, 1H); 7.43 (d, J = 5.8 Hz, 1H); 7.37-7.34 (m, 2H); 4.17-4.13 (m, 2H); 3.88 (s, 3H); 1.77-1.61 (m, 3H); 0.99 (d, J = 6.6 Hz, 6H). MS(ES+) m/e 448 $[M+H]^+$.

b) 4-Hydroxy-5-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one

The compound from Example 39a) (120 mg, 0.268 mmol) was suspended n 10 mL of AcOH. The mixture was warmed until a solution was obtained and then treated with 2 mL of 48% aq. HBr. After refluxing for 4 h, 1.5 mL of 48% aq HBr was added and the

mixture was stirred overnight at refluxing temperature, then treated with 2 mL of 48% aq HBr and refluxed for 2 h. After cooling to rt, the reaction mixture was poured into H_2O and the precipitate was collected, washed with H_2O, then Et_2O and dried to give the title compound (66 mg, 57%) as a brown powder. ^1H NMR (d_6-DMSO) δ 14.93 (br s,1H); 14.02 (br s, 1H); 10.41 (s, 1H); 7.57-7.55 (m, 1H); 7.48 (d, J = 5.8 Hz, 1H); 7.41 (d, J = 5.5 Hz, 1H); 7.17-7.15 (m, 2H); 4.16-4.12 (m, 2H); 1.77-1.60 (m, 3H); 0.98 (d, J = 6.5 Hz, 6H). MS(ES+) m/e 434 $[M+H]^+$.

Example 40

2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide

The compound from Example 38 (90 mg, 0.176 mmol) was suspended in DMF (2.5 mL) and warmed to 80 °C. Potassium carbonate (116 mg, 0.840 mmol) and 2-chloroacetamide (29.5 mg, 0.320 mmol) were then added to the solution and stirring was continued for 3.5 h at 80 °C. After cooling to rt, the reaction mixture was poured into 1N HCl, stirred for 10 min, and the solid obtained was collected, washed with H_2O, then Et_2O and dried to give the title compound (80 mg, 94%) as a off-white powder. ^1H NMR (d_6-DMSO) δ 15.15 (br s,1H); 14.03 (br s, 1H); 8.89 (dd, J = 4.6, 1.6 Hz, 1H); 8.55 (dd, J = 8.1, 1.7 Hz, 1H); 7.74 (d, J = 8.8 Hz, 1H); 7.67 (br s, 1H); 7.50 (dd, J = 8.0, 4.6 Hz, 1H); 7.46 (br s, 1H); 7.41 (d, J = 2.6 Hz, 1H); 7.38-7.37 (m, 1H); 4.60 (s, 2H); 4.50-4.46 (m, 2H); 1.74-1.63 (m, 1H); 1.59-1.54 (m, 2H); 0.98 (d, J = 6.6 Hz, 6H). MS(ES+) m/e 486 $[M+H]^+$.

Example 41

(R)-2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide

The compound from Example 38 (90 mg, 0.176 mmol) was suspended in DMF (2.5 mL) and warmed to 80 °C. Potassium carbonate (116 mg, 0.840 mmol) and (S)-2-*p*-tolyloxy-propionamide (102 mg, 0.420 mmol) were then added to the solution and stirring was continued for 1.5 h at 80 °C. After addition of 1 equivalent of potassium carbonate and 1 equivalent of (S)-2-*p*-tolyloxy-propionamide, stirring was continued overnight at 75 °C. After cooling to rt, the reaction mixture was poured into H_2O and the pH was adjusted to acidic by the addition of 1N HCl. The solid obtained was collected by filtration, washed with H_2O, then Et_2O and dried to give the title compound (75 mg, 85%) as an off-white

powder. ^{1}H NMR (d_6-DMSO) δ 15.15 (br s,1H); 14.00 (br s, 1H); 8.88 (dd, *J* = 4.5, 1.7 Hz, 1H); 8.55 (dd, *J* = 8.1, 1.7 Hz, 1H); 7.72 (d, *J* = 9.0 Hz, 1H); 7.70 (br s, 1H); 7.49 (dd, *J* = 8.1, 4.6 Hz, 1H); 7.37-7.34 (m, 2H); 7.30 (d, *J* = 2.7 Hz, 1H); 4.80 (q, *J* = 6.4 Hz, 1H); 4.50-4.46 (m, 2H); 1.74-1.64 (m, 1H); 1.59-1.53 (m, 2H); 1.47 (d, *J* = 6.6 Hz, 3H); 0.97 (d, *J* = 6.6 Hz, 6H). MS(ES+) m/e 500 $[M+H]^+$.

Example 42

2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide

The compound from Example 36d) (75 mg, 0.173 mmol) was suspended in DMF (2.5 mL) and warmed to 80 °C. Potassium carbonate (95.6 mg, 0.692 mmol) and 2-chloroacetamide (24.3 mg, 0.259 mmol) were then added to the solution and stirring was continued for 3.0 h at 80 °C. Additional potassium carbonate (0.5 equiv.) and 2-chloroacetamide (1 equiv.) were added and the reaction mixture was stirred for 2 h at the same temperature, then cooled, poured into water and made acidic by the addition of 1N HCl. The precipitate was collected, washed with H_2O, then Et_2O and dried to give the title compound (79 mg, 93%) as a gray powder. ^{1}H NMR (d_6-DMSO) δ 14.89 (br s,1H); 14.34 (br s, 1H); 8.37 (d, *J* = 5.5 Hz, 1H); 7.69-7.64 (m, 2H); 7.50 (d, *J* = 5.3 Hz, 1H); 7.46 (br s, 1H); 7.39-7.35 (m, 2H); 4.59 (s, 2H); 4.28-4.24 (m, 2H); 1.78-1.68 (m, 1H); 1.57-1.52 (m, 2H); 0.97 (d, *J* = 6.8 Hz, 6H). MS(ES+) m/e 491 $[M+H]^+$.

Example 43

(R)-2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide

The compound from Example 36d) (75 mg, 0.173 mmol) was suspended in DMF (2.5 mL) and warmed to 80 °C. Potassium carbonate (95.6 mg, 0.692 mmol) and (S)-2-*p*-tolyloxy-propionamide (84.2 mg, 0.346 mmol) were then added to the solution and stirring was continued for 1.0 h at 80 °C. Additional (S)-2-*p*-tolyloxy-propionamide (0.5 equiv.) was added, and the reaction mixture was stirred at 80 °C overnight. Additional potassium carbonate (1 equiv.) and 2-chloroacetamide (0.5 equiv.) were added and stirring was continued for 3.5 h at the same temperature. The reaction mixture was then cooled, poured into water and made acidic by the addition of 1N HCl. The precipitate was collected, washed with H_2O, then Et_2O and dried to give the title compound (74.5 mg, 85%) as a pale

yellow powder. ^{1}H NMR (d_6-DMSO) δ 14.89 (br s,1H); 14.33 (br s, 1H); 8.38 (d, J = 5.5 Hz, 1H); 7.69-7.66 (m, 2H); 7.51 (d, J = 5.3 Hz, 1H); 7.35-7.29 (m, 3H); 4.79 (q, J = 6.8 Hz, 1H); 4.28-4.24 (m, 2H); 1.78-1.68 (m, 1H); 1.57-1.52 (m, 2H); 1.46 (d, J = 6.5 Hz, 3H); 0.97 (d, J = 6.5 Hz, 6H). MS(ES+) m/e 505 $[M+H]^+$.

Example 44

2-{3-[4-Hydroxy-7-(3-methyl-butyl)-6-oxo-6,7-dihydro-thieno[2,3-b]pyridin-5-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide

The compound from Example 39b) (55 mg, 0.127 mmol) was suspended in DMF (2.0 mL) and warmed to 80 °C. Potassium carbonate (70.2 mg, 0.508 mmol) and 2-chloroacetamide (17.8 mg, 0.190 mmol) were then added to the solution and stirring was continued for 3.5 h at 80 °C. After addition of 2-chloroacetamide (0.5 equiv.) and stirring for 2 h, additional potassium carbonate (0.5 equiv.) and 2-chloroacetamide (0.5 equiv.) were added and the reaction mixture was stirred for 1 h at the same temperature. The mixture was then cooled to rt, poured into water and made acidic by the addition of 1N HCl. The precipitate was collected, washed with H_2O, then Et_2O and dried to give the title compound (43.6 mg, 70%) as a brown powder. ^{1}H NMR (d_6-DMSO) δ 14.84 (br s,1H); 14.08 (br s, 1H); 7.68 (d, J = 8.8 Hz, 1H); 7.66 (br s, 1H); 7.47 (d, J = 5.8 Hz, 1H); 7.45 (br s, 1H); 7.42-7.35 (m, 3H); 4.59 (s, 2H); 4.15-4.11 (m, 2H); 1.76-1.60 (m, 3H); 0.98 (d, J = 6.5 Hz, 6H). MS(ES+) m/e 491 $[M+H]^+$.

Example 45

1-(2-Cyclopropyl-ethyl)-4-hydroxy-3-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1H-[1,8]naphthyridin-2-one

a) 2-(2-Cyclopropyl-ethyl)-nicotinic acid

Potassium carbonate (28.1g, 203.2 mmol) was added to a solution of 2-chloronicotinic acid (10.0 g, 63.5 mmol) in DMF (150 mL). The mixture was stirred for 10 min and then 2-cyclopropyl-ethylamine hydrochloride (11.6 g, 95.2 mmol) was added, followed by copper powder (8.1 g, 127 mmol). The mixture was heated to reflux and stirred at this temperature overnight. The solvent was evaporated at reduced pressure, the residue was suspended in 85 mL of 2.5M NaOH, and the resulting copper precipitate was filtered off. The filtrate was acidified to pH 7 using 6N HCl, and the cloudy light green mixture was allowed to stand for one hour. The precipitate was collected, washed with water and ethanol/diethyl ether, and dried to give the title compound (2.7 g, 21%) as an off white powder. ^{1}H NMR (d_6-DMSO) δ 12.99 (br s, 1H); 8.24 (dd, J = 4.8, 2.0 Hz, 1H); 8.18 (br s, 1H); 8.04 (dd, J = 7.8, 2.0 Hz, 1H); 6.56 (dd, J = 7.6, 4.8 Hz, 1H); 3.50 (t, J = 6.8 Hz, 2H); 1.47 (q, J = 7.0 Hz, 2H); 0.76-0.66 (m, 1H); 0.44-0.39 (m, 2H); 0.10-0.06 (m, 2H).

b) 1-(2-Cyclopropyl-ethyl)-1*H*-pyrido[2,3-*d*][1,3]-oxazine-2,4-dione

Following the procedure from Example 1b), except substituting 2-(2-cyclopropyl-ethyl)-nicotinic acid for 2-(3-methyl-butyl)-nicotinic acid the title compound (1.17 g, 42%) was obtained as pale yellow crystals after trituration from Et_2O. ^{1}H NMR (d_6-DMSO) δ 8.77 (dd, J = 4.9, 1.9 Hz, 1H); 8.39 (dd, J = 7.7, 1.9 Hz, 1H); 7.38 (dd, J = 7.6, 4.8 Hz, 1H); 4.23-4.19 (m, 2H); 1.59-1.53 (m, 2H); 0.80-0.70 (m, 1H); 0.42-0.38 (m, 2H); 0.07-0.03 (m, 2H).

c) 1-(2-Cyclopropyl-ethyl)-4-hydroxy-3-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1H-[1,8]naphthyridin-2-one

DBU (0.496 mL, 3.32 mmol) was added dropwise to a solution of the compound from Example 45b) (350 mg, 1.51 mmol) and (7-hydroxy-1,1-dioxo-1,4-dihydro-benzo-[1,2,4]-thiadiazin-3-yl)-acetic acid ethyl ester (471 mg, 1.66 mmol) in DMF (10 mL). After stirring for 3 h at rt, an additional portion of the compound from Example 45b) (150 mg, 0.646 mmol) and stirring was continued at rt overnight. Acetic acid (3 mL) was then added and the reaction mixture was stirred for 3 h at rt, treated with 1 mL H_2O and poured into 1N

HCl. The precipitate was collected, washed with H_2O, the Et_2O and dried to give the desired product contaminated with 15% higher molecular weight impurity (384 mg, total weight). A portion of the material was triturated in hot 5% MeOH in $CHCl_3$, cooled, the solid collected by filtration, washed with $CHCl_3$ and dried to give the title compound as a off white powder. ^{1}H NMR (d_6-DMSO) δ 15.25 (br s,1H); 13.95 (br s, 1H); 10.43 (br s, 1H); 8.86 (dd, *J* = 4.5, 1.7 Hz, 1H); 8.54 (dd, *J* = 8.1, 1.7 Hz, 1H); 7.59 (d, *J* = 8.8 Hz, 1H); 7.48 (dd, *J* = 8.1, 4.6 Hz, 1H); 7.17-7.14 (m, 2H); 4.57-4.53 (m, 2H); 1.58 (q, *J* = 7.1 Hz, 2H); 0.79-0.69 (m, 1H); 0.38-0.34 (m, 2H); 0.03-(-)0.01 (m, 2H). MS(ES+) m/e 427 $[M+H]^+$.

Example 46

2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin 3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide

The compound from Example 45c) (55 mg, 0.129 mmol) was suspended in DMF (2.0 mL) and warmed to 80 °C. Potassium carbonate (71.3 mg, 0.516 mmol) and 2-chloroacetamide (18.1 mg, 0.193 mmol) were then added to the solution and stirring was continued for 3.0 h at 80 °C. Additional 2-chloroacetamide (0.5 equiv.) was then added and the mixture was stirred for 1.0 h at the same temperature. After cooling to rt, the reaction mixture was poured into H_2O and acidified by the addition of 1N HCl. The solid obtained was collected, washed with H_2O, then Et_2O and dried to give the title compound (56 mg, 90%) as a yellow powder. ^{1}H NMR (d_6-DMSO) δ 15.14 (br s,1H); 14.01 (br s, 1H); 8.85 (dd, *J* = 4.5, 1.7 Hz, 1H); 8.52 (dd, *J* = 7.9, 1.8 Hz, 1H); 7.69 (d, *J* = 8.8 Hz, 1H); 7.63 (br s, 1H); 7.46 (dd, *J* = 8.1, 4.6 Hz, 1H); 7.41 (br s, 1H); 7.38-7.33 (m, 2H); 4.56 (s, 2H); 4.56-4.51 (m, 2H); 1.56 (q, *J* = 7.4 Hz, 2H); 0.78-0.68 (m, 1H); 0.37-0.32 (m, 2H); 0.01-(-)0.02 (m, 2H). MS(ES+) m/e 484 $[M+H]^+$.

Example 47

(R)-2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide

The compound from Example 45c) (67.5 mg, 0.158 mmol) was suspended in DMF (2.0 mL) and warmed to 80 °C. Potassium carbonate (87.3 mg, 0.632 mmol) and (S)-2-*p*-tolyloxy-propionamide (77 mg, 0.316 mmol) were then added to the solution and the reaction mixture was stirred at 80 °C overnight. After addition of 0.5 equivalent of

potassium carbonate and 0.7 equivalent of (S)-2-*p*-tolyloxy-propionamide, stirring was continued for 2 h at the same temperature. After cooling to rt, the reaction mixture was poured into H_2O and the pH was adjusted to acidic by the addition of 1N HCl. The solid obtained was collected by filtration, washed with H_2O, then Et_2O and dried to give the title compound (66 mg, 84%) as an off-white powder. ^{1}H NMR (d_6-DMSO) δ 15.16 (br s,1H); 14.02 (br s, 1H); 8.88 (dd, *J* = 4.8, 1.7 Hz, 1H); 8.55 (dd, *J* = 8.0, 1.7 Hz, 1H); 7.73-7.70 (m, 2H); 7.49 (dd, *J* = 8.0, 4.7 Hz, 1H); 7.37-7.31 (m, 3H); 4.80 (q, *J* = 6.6 Hz, 1H); 4.57 (t, *J* = 7.4 Hz, 2H); 1.60 (q, *J* = 7.5 Hz, 2H); 1.47 (d, *J* = 6.5 Hz, 3H); 0.80-0.72 (m, 1H); 0.41-0.36 (m, 2H); 0.05-0.01 (m, 2H). MS(ES+) m/e 498 $[M+H]^+$.

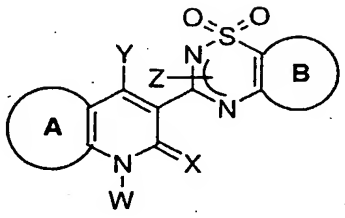
The HCV NS5B inhibitory activity of the compounds of Formula I was determined using standard procedures well known to those skilled in the art and described in, for example Behrens et al., EMBO J. 15:12-22 (1996), Lohmann et al., Virology 249:108-118 (1998) and Ranjith-Kumar et al., J. Virology 75:8615-8623 (2001).

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses how to make and use the present invention. However, this invention is not limited to the particular embodiments described hereinabove, but includes all modification thereof within the scope of the appended claims and their equivalents. Those skilled in the art will recognise through routine experimentation that various changes and modifications can be made without departing from the scope of this invention.

What is claimed is:

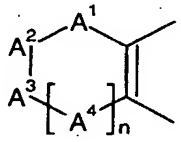
1. A compound according to Formula I:



I

wherein:

A is an accessible fused ring moiety that is an aromatic 6-membered carbocyclic ring moiety or a saturated, unsaturated or aromatic 5 or 6-membered heterocyclic ring moiety, wherein said heterocyclic ring moiety contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, represented by Formula II:



II

where:

A^1 is CR_A^1, CHR_A^1, N, NR_{A1}^5, O or S;

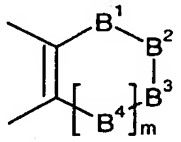
A^2 is CR_A^2, CHR_A^2, N, NR_{A2}^5, O or S;

A^3 is CR_A^3, CHR_A^3, N, NR_{A3}^5, O or S;

A^4 is CR_A^4, CHR_A^4, N, NR_{A4}^5, O or S;

n is 0 or 1;

B is an accessible fused ring moiety that is a 6-membered aromatic carbocyclic ring moiety or a saturated, unsaturated or aromatic 5 or 6-membered heterocyclic ring moiety, wherein said heterocyclic ring moiety contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, represented by the Formula III:



III

where:

B^1 is CR_B^1, CHR_B^1, N, NR_{B1}^5, O or S;

B^2 is CR_B^2, CHR_B^2 N, NR_{B2}^5, O or S;

B^3 is CR_B^3, CHR_B^3, N, NR_{B3}^5, O or S;

B^4 is CR_B^4, CHR_B^4, N, NR_{B4}^5, O or S;

m is 0 or 1;

or an N- or S-oxide thereof, provided that A and B are not both phenyl ring moieties;

wherein:

R_A^1 is hydrogen, halogen, C_1-C_4 alkyl, $-OR^{12}$, $-SR^{12}$, $-NR^{11}R^{12}$, -C(O)OH, $-C(O)NHR^{12}$, cyano or nitro;

R_A^2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, heterocycloalkyl, nitro, cyano, halogen, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-NR^{10}R^{11}$, protected -OH, $-N(R^{11})C(O)R^{10}$, $-OC(O)NR^{10}R^{11}$, $-N(R^{11})C(O)NR^{10}R^{11}$, $-P(O)(OR^{10})_2$, $-SO_2NR^{10}R^{11}$, $-SO_3H$, or $-N(R^{11})SO_2R^{13}$,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-NR^{11}R^{12}$, cyano, nitro, $-CO_2R^{11}$, $-C(O)OC_1$-C_4 alkyl, $-CONR^{11}R^{12}$, $-CONH_2$, aryl, and heteroaryl,

and where said cycloalkyl, heterocycloalkyl, aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -OH, -SH, $-NH_2$, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NH(C_1$-C_4 alkyl), cyano, nitro, $-CO_2H$, $-C(O)OC_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-CONH(C_1$-C_4 alkyl) and $-CONH_2$;

R_A^3 is hydrogen, halogen, cyano, C_1-C_6 alkyl, -OH, or $-CO_2H$;

R_A^4, R_B^4 and R_B^3 are each independently selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6 alkyl, -OH, and $-OC_1$-C_4 alkyl;

R_B^1 is hydrogen, halogen, hydroxyl or C_1-C_4 alkyl, $-OR^{10}$ or oxo;

R_B^2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, nitro, cyano, halogen, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-NR^{10}R^{11}$, protected -OH, $-N(R^{11})C(O)R^{10}$, $-OC(O)NR^{10}R^{11}$, $-N(R^{11})C(O)NR^{10}R^{11}$, $-P(O)(OR^{10})_2$, $-SO_2NR^{10}R^{11}$, $-SO_3H$, or $-N(R^{11})SO_2R^{13}$,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-NR^{11}R^{12}$, cyano, nitro, $-CO_2H$, $-C(O)OC_1$-C_4 alkyl,

-$CONR^{11}R^{12}$, -$CONH_2$, aryl, heteroaryl, heterocycloalkyl, -C(O)aryl, -C(O)heterocycloalkyl, and -C(O)heteroaryl, where said aryl, heteroaryl, heterocycloalkyl, aryl, -C(O)aryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OH, -SH, -NH_2, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano and nitro,

and where said cycloalkyl, heterocycloalkyl, aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -OH, -SH, -NH_2, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano, nitro, -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl) and -$CONH_2$;

or optionally, when A or B is an accessible heterocyclic ring moiety, one or more of $R_A{}^1$, $R_A{}^2$, $R_A{}^3$, $R_A{}^4$, $R_B{}^1$, $R_B{}^2$, $R_B{}^3$ and $R_B{}^4$ is oxo;

$R_{A1}{}^5$, $R_{A3}{}^5$, $R_{A4}{}^5$, $R_{B1}{}^5$, $R_{B3}{}^5$, $R_{B4}{}^5$ are each independently selected from: hydrogen, C_1-C_4 alkyl, -CO_2H, -$CONH_2$, -CO_2C_1-C_4 alkyl, -C(O)C_1-C_4 alkyl, -CONH(C_1-C_4 alkyl) and -C(O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl);

$R_{A2}{}^5$ and $R_{B2}{}^5$ is independently selected from the group consisting of H, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, -C(O)OR^{10}, -C(O)R^{10}, -S(O)R^{13}, -$S(O)_2R^{13}$, -$CONR^{10}R^{11}$, -P(O)$(OR^{10})_2$ and -$SO_2NR^{10}R^{11}$, where said alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halogen, cyano, -OR^{10}, -SR^{10}, -$NR^{10}R^{11}$, -C(O)OR^{10}, -$CONR^{10}R^{11}$, -S(O)R^{13}, -$S(O)_2R^{13}$ and -$SO_2NR^{10}R^{11}$; wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -CN and -NO_2;

W is hydrogen, -C(O)OR^{12}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkenyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkynyl)-(C_3-C_6 cycloalkyl), -(C_1-C_6 alkyl)-heterocycloalkyl, -(C_2-C_6 alkenyl)-heterocycloalkyl, -(C_2-C_6 alkynyl)-heterocycloalkyl, -(C_1-C_6 alkyl)-aryl, (C_2-C_6 alkenyl)-aryl, -(C_2-C_6 alkynyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl, -(C_2-C_6 alkenyl)-heteroaryl, or -(C_2-C_6 alkynyl)-heteroaryl,

where said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, -OH, -OC_1-C_4 alkyl, -SH, -SC_1-C_4 alkyl, -S(O)(C_1-C_4 alkyl), -SO_3H, and -S(O)$_2$(C_1-C_4 alkyl),

said C_3-C_6 cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_4 alkyl, -OH, -OC_1-C_4 alkyl, -SH, -SC_1-C_4 alkyl, -S(O)(C_1-C_4 alkyl), -SO_3H, and -S(O)$_2$(C_1-C_4 alkyl),

and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of said -(C_1-C_6 alkyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkenyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkynyl)-(C_3-C_6 cycloalkyl), -(C_1-C_6 alkyl)-heterocycloalkyl, -(C_2-C_6 alkenyl)-heterocycloalkyl, -(C_2-C_6 alkynyl)-heterocycloalkyl, -(C_1-C_6 alkyl)-aryl, (C_2-C_6 alkenyl)-aryl, -(C_2-C_6 alkynyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl, -(C_2-C_6 alkenyl)-heteroaryl, or -(C_2-C_6 alkynyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, cyano, nitro, -OH, -NH_2, -OC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -NH(C_1-C_4 alkyl);

X is O or S;

Y is -OH or -SH;

Z is hydrogen or C_1-C_4 alkyl;

wherein each R^{10} is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, and -C_1-C_6 alkyl-heteroaryl, -C_2-C_6 alkenyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkenyl-heterocycloalkyl, -C_2-C_6 alkenyl-aryl, -C_2-C_6 alkenyl-heteroaryl, -C_2-C_6 alkynyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkynyl-heterocycloalkyl, -C_2-C_6 alkynyl-aryl, and -C_2-C_6 alkynyl-heteroaryl,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OR^{12}, -$NR^{11}R^{12}$, cyano, nitro, -CO_2R^{12}, -$CONR^{11}R^{12}$, -$NR^{11}CONR^{11}R^{12}$, -$OCONR^{11}R^{12}$, -$SO_2NR^{11}R^{12}$, and -COR^{12},

and where any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl (including the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moieties of said -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, or -C_1-C_6 alkyl-heteroaryl) is unsubstituted or substituted with one or more substituents

independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, $-OR^{12}$, $-NR^{11}R^{12}$, cyano, nitro, $-CO_2R^{12}$, $-CONR^{11}R^{12}$, $-NR^{11}CONR^{11}R^{12}$, $-OCONR^{11}R^{12}$, $-SO_2NR^{11}R^{12}$, and $-COR^{12}$;

each R^{11} is independently selected from hydrogen and C_1-C_6 alkyl;

each R^{12} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_1$-C_4 alkyl-C_3-C_8 cycloalkyl, $-C_1$-C_4 alkyl-heterocycloalkyl, $-C_1$-C_4 alkyl-aryl, or $-C_1$-C_4 alkyl-heteroaryl

where said cycloalkyl, heterocycloalkyl, aryl , heteroaryl, -alkylcycloalkyl, -alkylheterocycloalkyl, -alkylaryl or -alkylheteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen $-OC_1$-C_6 alkyl, $-OC_1$-C_6 haloalkyl, cyano, $-N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), $-NH(C_1$-C_6 alkyl), $-NH_2$, $-CO_2C_1$-C_6 alkyl, $-CO_2H$, $-CON(C_1$-C_6 alkyl)(C_1-C_6 alkyl), $-CONH(C_1$-C_6 alkyl), and $-CONH_2$;

or, when present in any $NR^{10}R^{11}$ or $NR^{11}R^{12}$, each R^{10} and R^{11} or each R^{11} and R^{12}, independently, taken together with the nitrogen to which they are attached represent a 3-6-membered saturated ring optionally containing one other heteroatom selected from oxygen and nitrogen, where said 3-6-membered ring is unsubstituted or substituted with one or more substituents independently selected from hydrogen, C_1-C_6 alkyl, halogen, cyano, $-OC_1$-C_6 alkyl, -OH, $-N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), $-NH(C_1$-C_6 alkyl), $-NH_2$, $-CO_2H$, $-C(O)OC_1$-C_6 alkyl, $-C(O)C_1$-C_6 alkyl, $-CON(C_1$-C_6 alkyl)(C_1-C_6 alkyl), $-CONH(C_1$-C_6 alkyl), $-CONH_2$, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl-C_1-C_6 alkyl-, heterocycloalkyl-C_1-C_6 alkyl-, aryl-C_1-C_6 alkyl- and heteroaryl-C_1-C_6 alkyl-, and where said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl-, heterocycloalkylalkyl-, arylalkyl- or heteroarylalkyl- is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen $-OC_1$-C_6 alkyl, $-OC_1$-C_6 haloalkyl, cyano, $-N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), $-NH(C_1$-C_6 alkyl), $-NH_2$, $-CO_2C_1$-C_6 alkyl, $-CO_2H$, $-CON(C_1$-C_6 alkyl)(C_1-C_6 alkyl), $-CONH(C_1$-C_6 alkyl), and $-CONH_2$;

each R^{13} is independently selected from the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_1$-C_6 alkyl-C_3-C_8 cycloalkyl, $-C_1$-C_6 alkyl-heterocycloalkyl, $-C_1$-C_6 alkyl-aryl, and $-C_1$-C_6 alkyl-heteroaryl, $-C_2$-C_6 alkenyl-C_3-C_8 cycloalkyl, $-C_2$-C_6 alkenyl-heterocycloalkyl,

-C_2-C_6 alkenyl-aryl, -C_2-C_6 alkenyl-heteroaryl, -C_2-C_6 alkynyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkynyl-heterocycloalkyl, -C_2-C_6 alkynyl-aryl, and -C_2-C_6 alkynyl-heteroaryl,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OR^{14}, -$NR^{11}R^{14}$, cyano, nitro, -CO_2R^{14}, -$CONR^{11}R^{14}$, -$NR^{11}CONR^{11}R^{14}$, -$OCONR^{11}R^{14}$, -$SO_2NR^{11}R^{14}$, and -COR^{14},

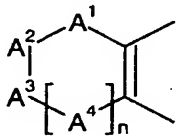
and where any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl (including the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moieties of said -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, or -C_1-C_6 alkyl-heteroaryl) is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OR^{14}, -$NR^{11}R^{14}$, cyano, nitro, -CO_2R^{14}, -$CONR^{11}R^{14}$, -$NR^{11}CONR^{11}R^{14}$, -$OCONR^{11}R^{14}$, -$SO_2NR^{11}R^{14}$, and -COR^{14};

each R^{14} is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, and -C_1-C_6 alkyl-heteroaryl;

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

2. The compound according to claim 1, wherein:

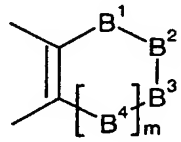
A is a fused ring moiety selected from a phenyl, pyrazolyl, pyridyl or thienyl ring moiety represented by



II

where when n is 0, A^1 is $CR_A{}^1$ or S, A^2 is $CR_A{}^2$, NH or N, and A^3 is $CR_A{}^3$, N, $NR_{A3}{}^5$ or S; or when n is 1, A^1 is $CR_A{}^1$, A^2 is $CR_A{}^2$, A^3 is $CR_A{}^3$, and A^4 is $CR_A{}^4$ or N; and

B is a fused ring moiety selected from a phenyl, pyridyl, piperidyl, thienyl or pyrazolyl ring moiety represented by



III

where when m is 0, B^1 is CR_B^1, B^2 is CR_B^2, NH or N, and B^3 is N, NR_{B3}^5 or S; or when m is 1; B^1 is CR_B^1 or CHR_B^1, B^2 is CR_B^2, CHR_B^2, N, N→O or NR_{B2}^5, B^3 is CR_B^3 or CHR_B^3, and B^4 is CR_B^4, CHR_B^4, or N;

or an N-oxide thereof, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

3. The compound according to claim 1, wherein

R_A^1 is hydrogen, halogen or C_1-C_4 alkyl;

R_A^2 is hydrogen, C_1-C_4 alkyl, nitro, cyano, halogen, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-NR^{10}R^{11}$, $-N(R^{11})C(O)R^{10}$, $-OC(O)NR^{10}R^{11}$, $-N(R^{11})C(O)NR^{10}R^{11}$, $-P(O)(OR^{10})_2$, $-SO_2NR^{10}R^{11}$, $-SO_3H$, or $-N(R^{11})SO_2R^{13}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, $-OC_1$-C_4 alkyl, $-SC_1$-C_4 alkyl, $-NR^{11}R^{12}$, cyano, nitro, $-C(O)R^{10}$, $-CO_2R^{11}$, $-C(O)OC_1$-C_4 alkyl, $-CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

R_A^3 is hydrogen, halogen, C_1-C_4 alkyl or $-CO_2H$;

R_A^4 is hydrogen, halogen or C_1-C_4 alkyl;

R_B^1 is hydrogen, halogen, hydroxyl, C_1-C_4 alkyl or $-OR^{10}$, or when B is a pyridyl, piperidyl, or pyrazolyl ring moiety, R_B^1 is hydrogen, halogen, hydroxyl, C_1-C_4 alkyl, $-OR^{10}$ or oxo;

R_B^2 is hydrogen, halogen, C_1-C_4 alkyl, $-C(O)OR^a$, $-OR^{b'}$, $-NR^aR^d$, $-C(O)NR^aR^d$, where said C_1-C_4 alkyl is unsubstituted or substituted with a substituent selected from of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-CO_2C_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is optionally unsubstituted or substituted with one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, R^a is H or methyl, $R^{b'}$ is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CON(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), 5-6 membered heterocycloalkyl or heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, and R^d is H, C_1-C_2 alkyl,

or phenyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl;

R_B^3 is hydrogen, halogen or C_1-C_4 alkyl or when B is a pyridyl, piperidyl, or pyrazolyl ring moiety, R_B^3 is hydrogen, halogen, C_1-C_4 alkyl or oxo;

R_B^4 is hydrogen, halogen, C_1-C_4 alkyl, -OH or -OC_1-C_4 alky;

R_{A1}^5, R_{A3}^5 and R_{A4}^5 are each independently selected from hydrogen, C_1-C_4 alkyl, -CO_2H, -CO_2C_1-C_4 alkyl and -C(O)C_1-C_4 alkyl;

R_{A2}^5 is hydrogen, C_1-C_4 alkyl, -C(O)OR^{10}, -C(O)R^{10}, -C(O)$NR^{10}R^{11}$, -S(O)R^{13}, -$S(O)_2R^{13}$, -$P(O)(OR^{10})_2$ or -$SO_2NR^{10}R^{11}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -$NR^{11}R^{12}$, cyano, -CO_2H, -C(O)OC_1-C_4 alkyl, -$CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

R_{B1}^5, R_{B3}^5 and R_{B4}^5 are each independently selected from hydrogen, C_1-C_4 alkyl, -CO_2H, -CO_2C_1-C_4 alkyl and -C(O)C_1-C_4 alkyl;

R_{B2}^5 is hydrogen, C_1-C_4 alkyl, -C(O)OR^{10}, -C(O)R^{10}, -$CONR^{10}R^{11}$, -$CON(R^{11})$phenyl, -S(O)R^{13}, -$S(O)_2R^{13}$, -$P(O)(OR^{10})_2$ or -$SO_2NR^{10}R^{11}$, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -$NR^{11}R^{12}$, cyano, -CO_2H, -C(O)OC_1-C_4 alkyl, -$CONR^{11}R^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

W is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_2 alkyl)-heterocycloalkyl, -(C_1-C_2 alkyl)aryl, -(C_1-C_2 alkyl)-heteroaryl, where said C_3-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, -OH, -OC_1-C_4 alkyl, -SH, -SC_1-C_4 alkyl, -S(O)(C_1-C_4 alkyl), -SO_3H, and -$S(O)_2$(C_1-C_4 alkyl), and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of said -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_2 alkyl)-heterocycloalkyl, -(C_1-C_2 alkyl)aryl, -(C_1-C_2 alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, cyano, nitro, -OH, -NH_2, -OC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -NH(C_1-C_4 alkyl);

each R^{10} may be independently selected from the group consisting of hydrogen and C_1-C_4 alkyl, where said C_1-C_4 alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -$NR^{11}R^{12}$, cyano, nitro, -CO_2H,

$-CO_2C_1$-C_4 alkyl, $-CONR^{11}R^{12}$, $-NR^{11}CONR^{11}R^{12}$, $-OCONR^{11}R^{12}$, $-SO_2NR^{11}R^{12}$, $-COR^{12}$, and monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

each R^{11} may be independently hydrogen or C_1-C_4 alkyl;

each R^{12} may be independently hydrogen, C_1-C_4 alkyl, or monocyclic cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

each R^{13} may be independently a C_1-C_4 alkyl group, which is optionally unsubstituted or substituted with one or more substituents independently selected from halogen, $-OR^{14}$, $-NR^{11}R^{14}$, cyano, nitro, $-CO_2R^{14}$, $-CONR^{11}R^{14}$, $-NR^{11}CONR^{11}R^{14}$, $-OCONR^{11}R^{14}$, $-SO_2NR^{11}R^{14}$, and $-COR^{14}$;

each R^{14} may be independently hydrogen or C_1-C_4 alkyl,

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

4. The compound according to claim 1, wherein:

$R_A{}^1$ is hydrogen or halogen;

$R_A{}^2$ is hydrogen, halogen, $-OR^b$ or $-NHR^b$, where R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -OH, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CONH(C_1$-C_2 alkyl) and 5-6 membered heterocycloalkyl or heteroaryl;

$R_A{}^3$ is H, halogen, or C_1-C_4 alkyl;

$R_A{}^4$ is hydrogen;

$R_B{}^1$ is hydrogen, halogen, C_1-C_4 alkyl or oxo;

$R_B{}^2$ is hydrogen, halogen, C_1-C_4 alkyl, $-C(O)OR^a$, $-OR^{b'}$, $-NR^aR^d$, $-C(O)NR^aR^d$, where said C_1-C_4 alkyl is unsubstituted or substituted with a substituent selected from of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-CO_2C_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is optionally unsubstituted or substituted with one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, R^a is H or methyl, $R^{b'}$ is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-C(O)OC_1$-C_2 alkyl, $-CON(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), 5-6 membered heterocycloalkyl or heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, and R^d is H, C_1-C_2 alkyl,

or phenyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl;

R_B^3 is hydrogen, halogen or C_1-C_4 alkyl;

R_B^4 is hydrogen, halogen or C_1-C_4 alkyl;

R_{A1}^5, R_{A2}^5, R_{A3}^5 and R_{A4}^5 are each independently selected from hydrogen, C_1-C_4 alkyl, $-CO_2H$, $-CO_2C_1$-C_4 alkyl and $-C(O)C_1$-C_4 alkyl;

R_{B1}^5, R_{B3}^5 and R_{B4}^5 are each independently selected from hydrogen, C_1-C_4 alkyl, $-CO_2H$, $-CO_2C_1$-C_4 alkyl and $-C(O)C_1$-C_4 alkyl;

R_{B2}^5 is hydrogen, a C_1-C_4 alkyl group, $-CO_2H$, $-CONH_2$, $-CO_2C_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl) or $-C(O)C_1$-C_4 alkyl, where said C_1-C_4 alkyl group is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, $-OC_1$-C_4 alkyl, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), cyano, $-CO_2H$, $-CO_2C_1$-C_4 alkyl, $-CONH_2$, $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), -CONH(phenyl), $-CON(C_1$-C_4 alkyl)(phenyl) and a 5-6 membered heterocycloalkyl or heteroaryl;

W is C_4-C_6 alkyl, C_4 alkenyl, C_4 alkynyl, $-(C_1$-C_2 alkyl$)$-$(C_3$-C_6 cycloalkyl), $-(C_1$ alkyl$)$-heterocycloalkyl, $-(C_1$ alkyl$)$-aryl, or $-(C_1$ alkyl$)$-heteroaryl, where the C_4-C_6 alkyl, C_4 alkenyl or C_4 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, $-OCH_3$, $-SCH_3$, and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of the $-(C_1$-C_4 alkyl$)$-$(C_3$-C_6 cycloalkyl), $-(C_1$-C_4 alkyl$)$-heterocycloalkyl, $-(C_1$-C_4 alkyl$)$-heterocycloalkyl, $-(C_1$-C_4 alkyl$)$-aryl, or $-(C_1$-C_4 alkyl$)$-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from $-CH_3$, halogen, nitro, cyano, $-OR^a$, $-NR^aR^a$, where , each R^a is independently H or methyl,

or a tautomer thereof, or a salt or solvate thereof.

5. The compound according to any one of claims 1-4, wherein X is O, Y is OH.

6. The compound according to any one of claims 1-4, wherein Z is H.

7. The compound according to claim 5 or claim 6, wherein:

R_A^1, R_A^3 and R_A^4 are each H;

R_A^2 is H, Br, F, -OH or $-OCH_2CN$;

R_{A1}^5 and R_{A4}^5 are not present;

R_{A2}^5 is H or R_{A3}^5 is H or CH_3;

R_B^1 is H, Br, or $-CH_3$, or, when B is a fused piperidyl ring moiety, R_B^1 is H or oxo;

R_B^2 is H, Cl, -OH, $-OCH_3$, $-OCH_2CONH_2$, $-OCH(CH_3)CONH_2$ or $-OCH(R\text{-}CH_3)CONH_2$;

R_B^3 and R_B^4 are each H;

R_{B1}^5 and R_{B4}^5 are not present;

R_{B2}^5 is H, $-CH_2CH_3$, $-(CH_2)_3NH_2$, $-(CH_2)_2CN$, $-(CH_2)_2CONH_2$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-(CH_2)_2$-tetrazol-5-yl, $-CONHCH_3$, -CONH(phenyl) or $-C(O)CH_3$;

R_{B3}^5 is CH_3;

W is $-(CH_2)_2CH(CH_3)_2$, $-(CH_2)_2C(CH_3)_3$, $-(CH_2)_2CH(CH_3)CH_2CH_3$, $-(CH_2)_2$(cyclopropyl) or $-CH_2$(3-tetrahydrofuryl);

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

8. A compound according to any one of claims 1-7, wherein

A is a substituted or unsubstituted phenyl, pyridyl, pyrazolyl or thienyl ring moiety, wherein when n is 0, A^1 is CH or S, A^2 is CR_A^2, N, and A^3 is CH, NH, N-C_1-C_4 alkyl or S; or when n is 1, A^1 is CH, A^2 is CR_A^2, A^3 is CH, and A^4 is CH or N;

B is a substituted or unsubstituted phenyl, pyridyl, piperidyl, pyrazolyl or thienyl ring moiety, wherein when n is 0, B^1 is CR_B^1, B^2 is N or CR_B^2, and B^3 is N, N-C_1-C_4 alkyl or S; or when n is 1: B^1 is CH, CH_2 or C=O; B^2 is CR_B^2, N, N→O or NR_{B2}^5, B^3 is CH, CH_2 or $CH(CH_3)$ and B^4 is CH, CH_2 or N;

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

9. A compound according to any one of claims 1-7, wherein A is a substituted or unsubstituted phenyl, pyridyl, or thienyl ring moiety, wherein when n is 0, A^1 is CH or S, A^2 is CR_A^2, and A^3 is CH or S; or when n is 1, A^1 is CH, A^2 is CR_A^2, A^3 is CH, and A^4 is CH or N; and B is a substituted or unsubstituted phenyl, pyridyl, piperidyl, or thienyl ring moiety, wherein when n is 0, B^1 is CH, B^2 is CR_B^2, and B^3 is S; or when n is 1: B^1 is CH, CH_2 or C=O; B^2 is CR_B^2, N, N→O or NR_{B2}^5, B^3 is CH or CH_2 and B^4 is CH, CH_2 or N; provided A and B are not both phenyl;

or a tautomer thereof, or a pharmaceutically aceptable salt or solvate thereof.

10. A compound selected from the group consisting of:

3-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-naphthiridin-2-one,

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

1-(3,3-Dimethyl-butyl)-3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one,

(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-[1,8]napthyridin-2-one,

1-(3,3-Dimethyl-butyl)-3-(1,1-dioxo-4*H*-1,4-dihydropyrido[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one,

6-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadizine-3-yl)-7-hydroxy-4-(3-methyl-butyl)-4*H*-thieno[3,2-*b*]pyridin-5-one,

5-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadizine-3-yl)-4-hydroxy-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one,

2-Bromo-5-(1,1-dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadizine-3-yl)-4-hydroxy-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one,

3-(7-Bromo-6-Chloro-1,1-dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(6-Chloro-1,1-dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(5,7-Dimethyl-1,1-dioxo-4*H*-1,4-dihydro-5*H*-pyrazo[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(1,1-Dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(tetrahydro-furan-3-ylmethyl)-1H-quinolin-2-one,

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-pentyl)-1H-quinolin-2-one,

3-(1,1-Dioxo-1,4,5,6,7,8-hexahydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(7-Acetyl-1,1-dioxo-1,4,5,6,7,8-hexahydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1*H*-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-acetic acid methyl ester,

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-propionitrile,

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-acetic acid,

3-[7-(3-Amino-propyl)-1,1-dioxo-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

3-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

{3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazin-7-yl}-propionamide,

5-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-methyl-7-(3-methyl-butyl)-1,7-dihydro-pyrazolo[3,4-b]pyridin-6-one,

5-(1,1-Dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-7-(3-methyl-butyl)-1,7-dihydro-pyrazolo[3,4-b]pyridin-6-one,

3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazine-7-carboxylic acid phenylamide,

3-[4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-4,5,6,8-tetrahydro-1H-pyrido[4,3-e][1,2,4]thiadiazine-7-carboxylic acid methylamide,

3-[7-Ethyl-1,1-dioxo-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

3-(1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4,6-dihydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

3-[1,1-Dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-6-yloxy]-acetonitrile,

3-{1,1-Dioxo-7-[2-(2H-tetrazol-5-yl)-ethyl]-1,4,5,6,7,8-hexahydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl}-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-quinolin-3-yl]-1,1-dioxo-1,7-dihydro-4H-116-pyrido[4,3-e][1,2,4]thiadiazin-8-one,

3-(1,1-Dioxo-7-oxy-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1H-quinolin-2-one,

1-(2-Cyclopropyl-ethyl)-3-(1,1-dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-6-flu oro-4-hydroxy-1H -quinolin-2-one,

1-(2-Cyclopropyl-ethyl)-3-(1,1-dioxo-1,4-dihydro-pyrido[2,3-e][1,2,4]thiadiazin-3-yl)-6-fluoro-4-hydroxy-1H-quinolin-2-one,

7-Hydroxy-6-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-4-(3-methyl-butyl)-4H-thieno[3,2-b]pyridin-5-one,

4-Hydroxy-3-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1-(3-methyl-butyl)-1H-[1,8]naphthyridin-2-one,

4-Hydroxy-3-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1-(3-methyl-butyl)-1H-[1,8]naphthyridin-2-one,

4-Hydroxy-5-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-7-(3-methyl-butyl)-7H-thieno[2,3-b]pyridin-6-one,

2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

(R)-2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

(R)-2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

2-{3-[4-Hydroxy-7-(3-methyl-butyl)-6-oxo-6,7-dihydro-thieno[2,3-b]pyridin-5-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

1-(2-Cyclopropyl-ethyl)-4-hydroxy-3-(7-hydroxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-1H-[1,8]naphthyridin-2-one,

2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin 3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide, and

(R)-2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide;

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

11. A pharmaceutically acceptable salt of the compound according to claim 10, or tautomer thereof, wherein said pharmaceutically acceptable salt is a sodium salt or a potassium salt.

12. A compound according to claim 10 selected from the group consisting of:

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

1-(3,3-Dimethyl-butyl)-3-(1,1-Dioxo-4*H*-1,4-dihydropyrido[4,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-[1,8]naphthiridin-2-one,

6-(1,1-Dioxo-4*H*-1,4-dihydrobenzo[1,2,4]thiadizine-3-yl)-7-hydroxy-4-(3-methyl-butyl)-4*H*-thieno[3,2-*b*]pyridin-5-one,

3-(6-Chloro-1,1-dioxo-4*H*-1,4-dihydrothieno[2,3-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1-(3-methyl-butyl)-1*H*-quinolin-2-one,

1-(2-Cyclopropyl-ethyl)-3-(1,1-dioxo-1,4-dihydro-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-6-fluoro-4-hydroxy-1H -quinolin-2-one,

2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

(R)-2-{3-[4-Hydroxy-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

(R)-2-{3-[7-Hydroxy-4-(3-methyl-butyl)-5-oxo-4,5-dihydro-thieno[3,2-b]pyridin-6-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide,

2-{3-[4-Hydroxy-7-(3-methyl-butyl)-6-oxo-6,7-dihydro-thieno[2,3-b]pyridin-5-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide,

2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin 3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-acetamide, and

(R)-2-{3-[1-(2-Cyclopropyl-ethyl)-4-hydroxy-2-oxo-1,2-dihydro-[1,8]naphthyridin-3-yl]-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-7-yloxy}-propionamide;

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

13. A pharmaceutically acceptable salt of the compound according to claim 12, or tautomer thereof, wherein said pharmaceutically acceptable salt is a sodium salt or a potassium salt.

14. A method of inhibiting an RNA-containing virus which comprises contacting said virus with an effective amount of the compound according to any one of claims 1 to 13.

15. A method of treating infection caused by an RNA-containing virus which comprises administering to a subject in need thereof an effective amount of the compound according to any one of claims 1 to 13.

16. A method according to claim 15 comprising treating an HCV infection.

17. A method according to claim 14 or claim 15 comprising inhibiting hepatitis C virus.

18. A method according to claim 15, wherein said HCV infection is acute hepatitis infection, chronic hepatitis infection, hepatocellular carcinoma or liver fibrosis.

19. A method according to claim 15 comprising treating an infection caused by Dengue, HIV or a picornavirus.

20. A method according to claim 15 comprising administering said compound in combination with one or more agents selected from the group consisting of an immunomodulatory agent and an antiviral agent.

21. A method according to claim 20, wherein the immunomodulatory agent is selected from the group consisting of alpha interferon, beta interferon, gamma interferon, a cytokine, a vitamin, a nutritional supplement, an antioxidant compound, a vaccine and a vaccine comprising an antigen and an adjuvant.

22. A method according to claim 15 comprising administering said compound in combination with an interferon.

23. A method according to claim 15 comprising administering said compound in combination with an interferon and ribavirin.

24. A method according to claim 15 comprising administering said compound in combination with an interferon and levovirin.

25. A method according to claim 15 comprising administering said compound in combination with an HCV antisense agent.

26. A method according to claim 15 comprising administering said compound in combination with an immunoglobulin, a peptide-nucleic acid conjugate, an oligonucleotide, a ribozyme, a polynucleotide, an anti-inflammatory agent, a pro-inflammatory agent, an antibiotic or a hepatoprotectant.

27. A method for inhibiting replication of hepatitis C virus comprising inhibiting replication of both positive and negative strand HCV-RNA, said method comprising contacting a cell infected with said virus with an effective amount of the compound according to any one of claims 1 to 13.

28. A method of treating infection caused by hepatitis C virus comprising inhibiting replication of both positive and negative strand HCV-RNA, said method comprising administering to a subject in need thereof an effective amount of the compound according to any one of claims 1 to 13.

29. The method according to claim 27, wherein said compound substantially equally inhibits positive strand HCV-RNA replication and negative strand HCV-RNA replication.

30. The method according to claim 28, wherein said compound substantially equally inhibits positive strand HCV-RNA replication and negative strand HCV-RNA replication.

31. Use of the compound according to claim 1, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of an RNA-containing virus.

32. Use of the compound according to claim 1, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament that inhibits hepatitis C virus.

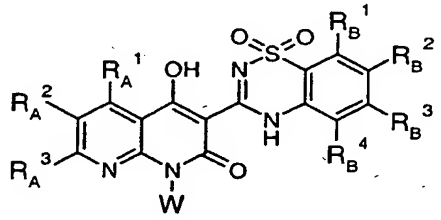
33. Use of the compound according to claim 1, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament that inhibits replication of both positive and negative strand HCV-RNA.

34. A compound selected from the group consisting of:

2-(3-methyl-butylamino)-nicotinic acid, 1-(3-methyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione, 2-(-3,3-dimethyl-butylamino)-nicotinic acid, 1-(3,3-dimethyl-butyl)-1H-pyrido[2,3-d][1,3]-oxazine-2,4-dione, 1-(3,3-dimethyl-butyl)-4-hydroxy-2-oxo-1,2-dyhydro-[1,8]napthyridine-carbonitrile, 1-(3,3-dimethyl-butyl)-4-hydroxy-2-oxo-1,2-dyhydro-[1,8]napthyridine-carboxamidine, 1-(3-methyl-butyl)-1H-thieno[3,2-d][1,3]oxazine-2,4-dione, 1-(3-Methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione, 6-bromo-1-(3-methyl-butyl)-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione, 4-hydroxy-2-oxo-1-(tetrahydro-furan-3-ylmethyl)-1,2-dihydro-quinoline-3-carbonitrile, 4-hydroxy-2-oxo-1-(tetrahydro-furan-3-ylmethyl)-1,2-dihydro-quinoline-3-carboxamidine, 4-hydroxy-1-(3-methyl-pentyl)-2-oxo-1,2-dihydro-quinoline-3-carbonitrile, 4-hydroxy-1-(3-methyl-pentyl)-2-oxo-1,2-dihydro-quinoline-3-carboxamidine, (1,1-dioxo-1,4-dihydro-1-thia-2,4,8-triaza-naphthalen-3-yl)-acetic acid ethyl ester, ethyl 1-methyl-5-(3-methyl-butylamino)-1*H*-pyrazole-4-carboxylate, (1,1-dioxo-1,4-dihydro-1-pyrido[4,3-e][1,2,4]thiadiazin-3-yl)-acetic acid ethyl ester, 1-(2-cyclopropyl-ethyl)-6-fluoro-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonitrile, 1-(2-cyclopropyl-ethyl)-6-fluoro-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxamidine, 7-hydroxy-6-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-

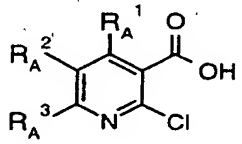
yl)-4-(3-methyl-butyl)-4*H*-thieno[3,2-*b*]pyridin-5-one, 4-hydroxy-5-(7-methoxy-1,1-dioxo-1,4-dihydro-benzo[1,2,4]thiadiazin-3-yl)-7-(3-methyl-butyl)-7*H*-thieno[2,3-*b*]pyridin-6-one, 2-(2-cyclopropyl-ethyl)-nicotinic acid, 1-(2-cyclopropyl-ethyl)-1*H*-pyrido[2,3-*d*][1,3]-oxazine-2,4-dione, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

35. A process for the preparation of the compound according to claim 1 having the Formula:

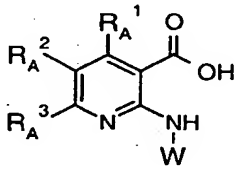


comprising the steps of:

a) treating a compound having the formula:

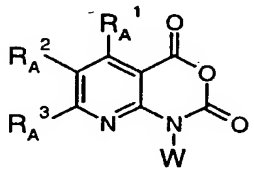


with an amine to form a compound having the formula:



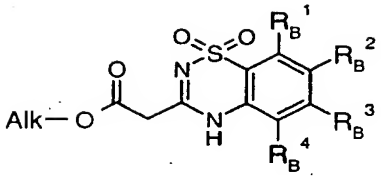
;

b) converting the compound formed in step a) into a heteroaryloxazine-2,4-dione having the formula:



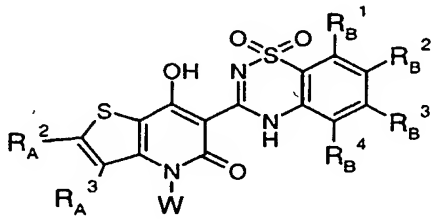
; and

c) treating the heteroaryloxazine-2,4-dione with a substituted (1,1-dioxo-dihydrobenzo-[1,2,4]-thiadiazin-3-yl)-acetic acid alkyl ester having the formula:



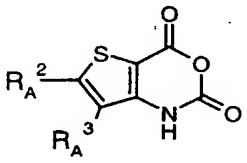
to form said compound.

36. A process for the preparation of the compound according to claim 1 having the Formula:

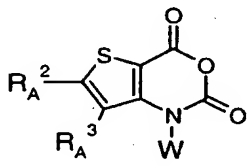


comprising the steps of:

a) treating a compound having the formula:

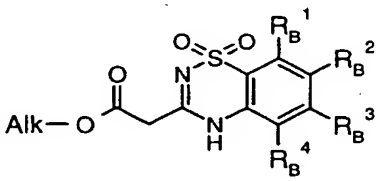


with an alkyl halide or an alkanol to form a heteroaryloxazine-2,4-dione having the formula:



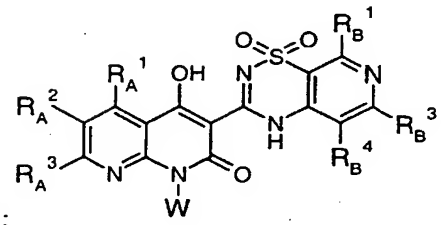
; and

b) treating the heteroaryloxazine-2,4-dione with a substituted (1,1-dioxo-dihydrobenzo-[1,2,4]-thiadiazin-3-yl)-acetic acid alkyl ester having the formula:



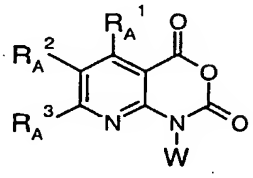
to form said compound.

37. A process for the preparation of the compound according to claim 1 having the Formula:

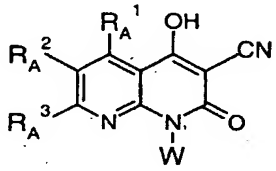


comprising the steps of:

a) converting a compound having the formula:

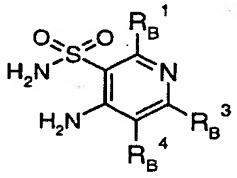


into a compound having the formula:



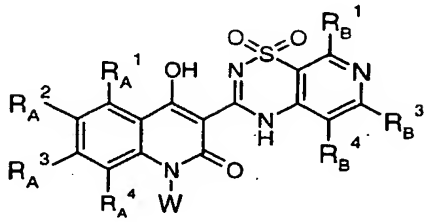
; and

b) treating the compound formed in step a) with an ortho-amino-heteroaryl sulfonic acid amide having the formula:



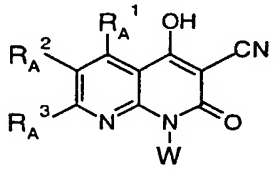
to form said compound.

38. A process for the preparation of the compound according to claim 1 having the Formula:

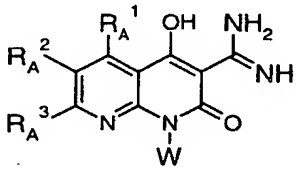


comprising the steps of:

a) converting a compound having the formula:

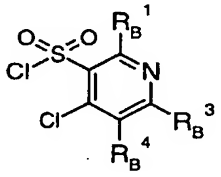


into an amidine compound having the formula



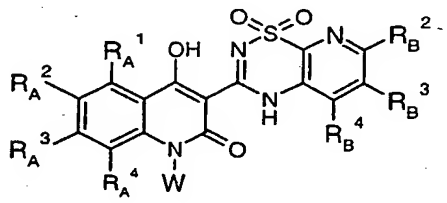
; and

b) treating the amidine compound formed in step a) with an ortho-chloro-heteroarylsulfonyl chloride having the formula:



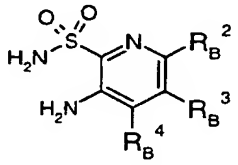
to form said compound.

39. A process for the preparation of the compound according to claim 1 having the Formula:

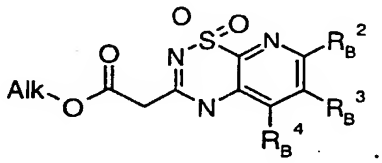


comprising the steps of:

a) treating a compound having the formula:

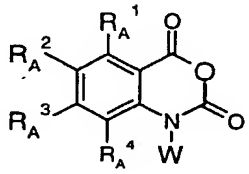


with a 3,3,3-trialkoxy-propionic acid alkyl ester to form a compound having the formula



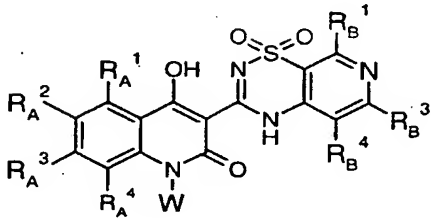
; and

b) treating the compound formed in step a) with an aryloxazine-2,4-dione having the formula:



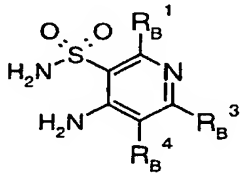
to form said compound.

40. A process for the preparation of the compound according to claim 1 having the Formula:

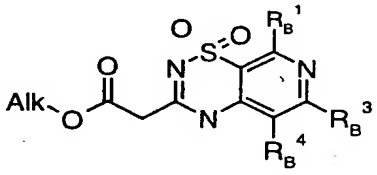


comprising the steps of:

a) treating a compound having the formula:

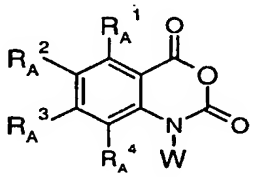


with a 3,3,3-trialkoxy-propionic acid alkyl ester to form a compound having the formula



; and

b) treating the compound formed in step a) with an aryloxazine-2,4-dione having the formula:



to form said compound.

SEQUENCE LISTING

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<151> 2001-10-30

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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; PO Box 7929, One Franklin Plaza, Philadelphia, PA 19101 (US).

(72) Inventors; and

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(74) Agent: **SIEBURTH, Kathryn, L.**; UW2220, 709 Swedeland Road, King Of Prussia, PA 10406 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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22 January 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/059356 A3

(54) Title: NOVEL ANTI-INFECTIVES

(57) Abstract: Disclosed are compounds useful as HCV anti-infectives and methods of making and using the same.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/34591

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/542; C07D 513/04
US CL : 514/223.2; 544/12, 13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/223.2; 544/12, 13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN/CAS, structure search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database CAPLUS on STN, AN 2000:335217.Chem abstr., Vol. 133, 2000 (Columbus, OH, USA), abstract 335217, UKRAINETS et al., '4-Hydroxy-2-Quinolones. Part 42. Synthesis and Biological Activity of 1-Substituted 2-Oxo-3-(2H-1,2,4-Benzothiadiazine-1,1,-dioxid-3-yl)-4-Hydroxyquinolines.' Chemistry of Heterocyclic Compounds (New York), 2000, 36(3), 346-350.	1-6, 10-13, 31-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
17 June 2003 (17.06.2003)

Date of mailing of the international search report
01 JUL 2003

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer
Richard L. Raymond

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/34591

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claim Nos.: 7-9 and 14-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.